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SCIENCE

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AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

What General Electric People Are Saying...

C. H. LANG

Mr. Lang is Vice President in charge of Public Relations

". . . In large measure, our Puritan ancestors insisted that liberty was dependent upon the general education of the country's citizenry. Our industrial system, as we know it today, is dependent on the education of that same citizenry. If we lose sight of this fact, we also lose sight of the fact that under a totalitarian system every industrial plan, or scientific research plan, becomes a State-plan. Every manager in industry becomes, in reality, a civil servant. Political democracy and industrial democracy depend on each other, and both depend on education.

There are two great educational objectives in America. First, we must endeavor to combine the British concern for training the "natural aristocracy of talents" with: Second, the American tradition and insistence of general education for *all* future citizens. If we can do this, then our industrial society will prosper, and at the same time the necessary degree of instruction will be provided for all people so that in their hands "our liberties will remain secure."

at a Meeting of Charles Coffin and Gerard Swope Fellows, Schenectady, New York

L. P. GROBEL

Mr. Grobel is Supervisor, Generator Mechanical Engineering, Large Steam Turbine and Generator Department, Turbine Division

". . . Precision balanced rotors have given smoother running turbine-generators with a great reduction in the amount of balancing needed at installation. High-speed 3600-rpm units placed in operation in 1949 had an average bearing vibration of 0.42 mils. By contrast, in 1950, when many of the present precision-balancing practices were adopted, this figure dropped to 0.30 mils. And during the years 1950 and 1952, it has remained nearly constant at 0.26 and 0.27 mils, respectively.

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G.E. Review

HERBERT SCHREIBER, JR.

Mr. Schreiber is an Industrial Product Engineer, General Electric X-Ray Department

". . . The first and obvious requisite for cathode-ray sterilization is the penetration or accelerating voltage required for the product and container size. Here two factors control the ultimate decision; namely, 1) Is complete penetration required or will surface sterilization be sufficient? 2) Can the physical dimensions of the product to be irradiated be changed for a more practical solution? The question of complete sterilization as opposed to surface sterilization can only be answered by the ultimate aim of the user. In many cases it is only desired to extend the shelf life of the product and a surface sterilization will often accomplish this purpose. In addition the severity of any organoleptic changes is usually increased with higher penetration thereby making higher voltage a detriment rather than an aid. Of course, if complete sterility is required then the cathode-ray generator must necessarily have sufficient voltage to penetrate the entire sample. The only alternative here is a change in the thickness or mode of packaging of the product thereby decreasing the ultimate penetration required. The factors controlling this decision are the additional costs of higher voltage equipment as opposed to the costs of changes in product dimensions or packaging technics.

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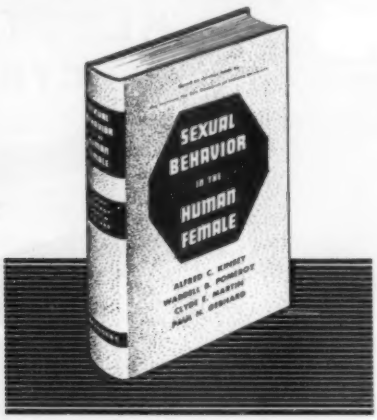

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This is the only report on female sexual behavior written or authorized by Dr. Kinsey and his associates. Neither the authors nor the publisher has any connection with, or any control over, any other volume on the subject which may appear.

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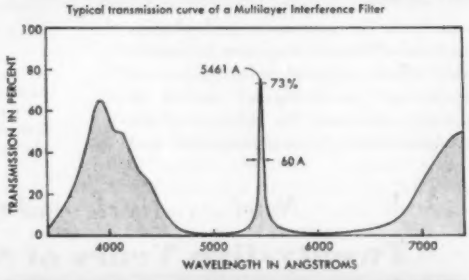

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IN Great Britain the cause of physics is furthered by the Physical Society, membership of which is open to anyone interested in physics and its development. The Physical Society was founded in 1873 by a group of physicists wishing to discuss their various problems together, and from this small beginning it has grown to a present membership of about 2000.

The activities fall into three main groups, its publications, its meeting, and its Annual Exhibition. The two main publications of the Society are the *Proceedings of the Physical Society,* which is published monthly, and the *Reports on Progress in Physics,* which is published annually. In the Proceedings are published papers describing original research in all branches of physics—nuclear physics, magnetism, semi-conductors, acoustics, and optics—by workers in universities, research associations, and research laboratories of large firms. The Reports on Progress in Physics contain about nine or ten articles by specialists describing the recent progress and present position in various fields in such a way that they can be read with interest and profit by the non-specialist.

These publications are available for sale in the general market and are also available to Members of the Society at greatly reduced rates. The Society has also a Reprint Service whereby members of the Society and subscribers to the Proceedings can purchase reprints of individual articles published in the Proceedings.

The Physical Society holds from three to six one or two day Conferences annually in various parts of the British Isles. These usually center around a university or research establishment where work in a certain field is in progress and opportunity is afforded for other workers in the same field to meet together to discuss problems, both theoretical and experimental.

The Society also sponsors the activities of specialist groups in color, optics, low temperature physics, and acoustics. These groups have a central core of interest in physics but extend their activities into other fields, for instance, the Acoustics Group is interested in architectural acoustics, the Color Group in the physiological aspects of color, and so on. These groups hold their own meetings, mainly in London, and often cooperate very successfully with sister societies whose interests meet theirs from another direction.

The third major activity of the Physical Society is its Annual Exhibition of Scientific Instruments and Apparatus at which a number of British firms and research organizations are invited to show instruments of use to the physicist which they have recently developed or are still in the process of developing. Visitors come to this Exhibition from all parts of the world and find the handbook published in connection with it of great value, not only when inspecting the exhibits but also to have upon their shelves as a work of reference giving a comprehensive survey of new developments in British scientific instrument work.

The Physical Society is anxious to increase its contacts with other parts of the world, and in particular with the United States of America, and welcomes this opportunity to describe its activities.

A. C. STICKLAND

The Physical Society, London

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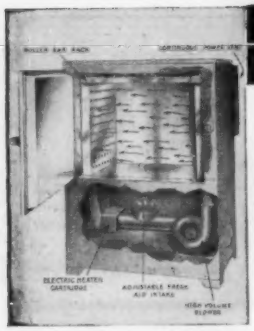

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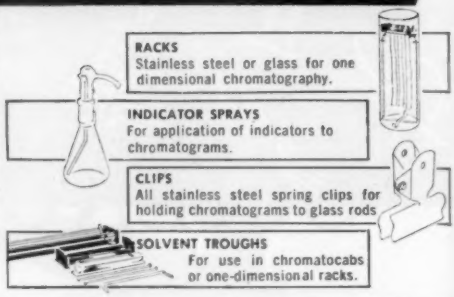

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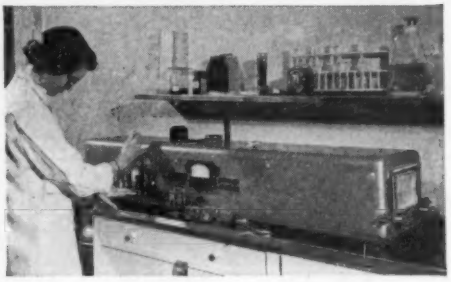

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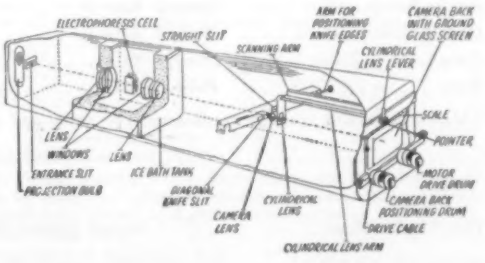

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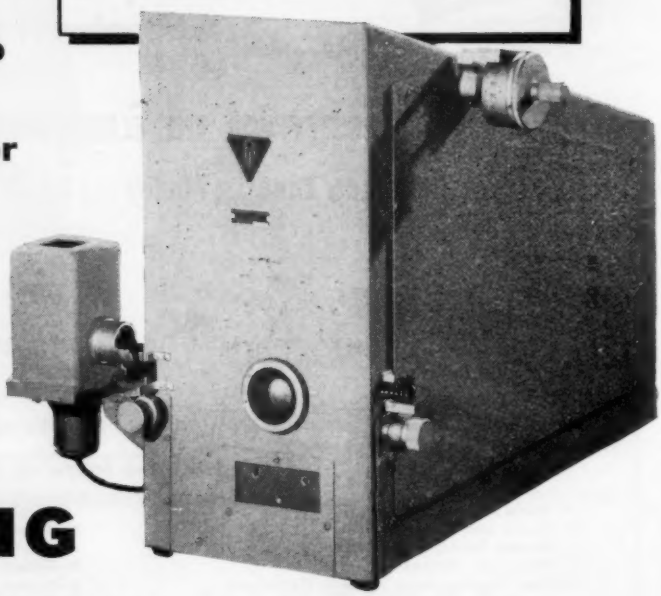

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Institute of Microbiology, Rutgers University, New Brunswick, New Jersey

The Lord hath created medicines out of the earth; and he that is wise will not abhor them. Ecclesiastes XXXVIII, 4.

THE HIGHEST SCIENTIFIC AWARD AND HONOR presented to me today gives me the opportunity to summarize briefly the discovery and utilization of streptomycin for disease control, notably in the treatment of tuberculosis, the "Great White Plague" of man.

Historical Background

Streptomycin belongs to a group of compounds, known as antibiotics, which are produced by microorganisms and which possess the property of inhibiting the growth of, and even of destroying, other microorganisms. Antibiotics vary greatly in their chemical nature, mode of action upon different organisms, and effect upon the animal body. The selective action of antibiotics upon bacteria and other microorganisms is known as the antibiotic spectrum. Some antibiotics are characterized by a very narrow spectrum, whereas others possess a wide range of activity. Some are active only against certain bacteria and not against others, whereas some are active against fungi, and some against viruses. There is not only considerable qualitative variation in the activity of different antibiotics, but also wide quantitative differences. Antibiotics are produced by bacteria, fungi, actinomycetes, and, to a limited extent, by other groups of microorganisms.

It has been known for more than six decades that certain fungi and bacteria are capable of producing chemical substances which have the capacity to inhibit the growth of, and even to destroy, pathogenic organisms. Only within the last twelve or thirteen years, however, have antibiotics begun to find extensive application as chemotherapeutic agents. Among these, penicillin and streptomycin have occupied a prominent place. Penicillin is largely active against gram-positive bacteria, gram-negative cocci, anaerobic bacteria, spirochetes and actinomycetes; streptomycin is active against a variety of gram-negative and acid-fast bacteria, as well as against gram-positive organisms which have become resistant to penicillin. Neither of these antibiotics is active upon rickettsiae, viruses, and fungi. They differ too in their physical and chemical properties and in their toxicity to animals.

Since the discovery of streptomycin, the production and clinical application of this antibiotic have had a

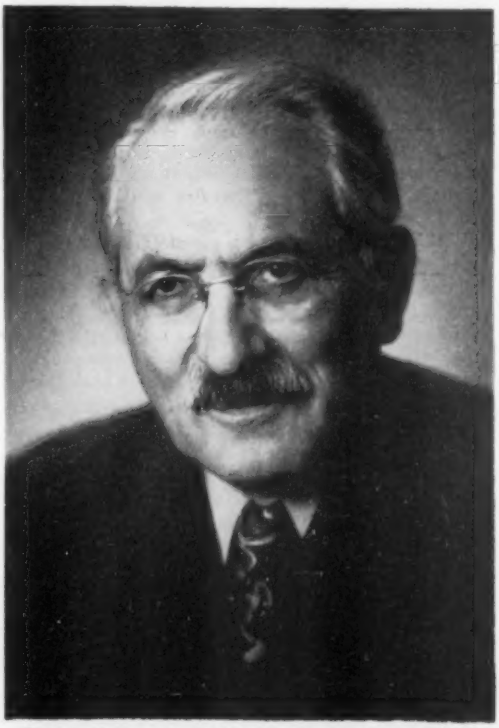

FIG. 1. Selman A. Waksman, Nobel Prize laureate for Physiology and Medicine for 1952.

[1] Nobel Prize Address, delivered at the Caroline Institute in Stockholm, Sweden, on December 12, 1952.

[2] I wish to take this opportunity to thank all my collaborators, associates, and graduate students who have participated in the investigations necessary to the development of our broad antibiotic program. Special thanks are due to the following assistants and graduate students: Misses Elizabeth S. Horning, Elizabeth Bugie, Doris Jones, D. Hutchison, H. C. Reilly and Dorothy G. Smith; Drs. M. Welsch, W. Geiger, W. Garson and E. A. Swart; and Messrs. H. B. Woodruff, Albert Schatz, H. Lechevalier, S. R. Green, D. A. Harris, W. P. Iverson, D. Reynolds, H. J. Robinson, and Otto Graessle; to the chemists, pharmacologists, bacteriologists, and engineers of Merck & Co.; to Drs. W. H. Feldman and H. C. Hinshaw of the Mayo Clinic; to Dr. C. S. Keefer of the Committee on Medical Research; and to numerous clinical investigators who have helped to make streptomycin the important chemotherapeutic agent it is today.

phenomenal rise. The streptomycin-producing strain of *Streptomyces griseus* was isolated in September, 1943, and the first public announcement of the antibiotic was made in January, 1944. Before the end of that year, streptomycin was already being submitted to clinical trial. Within 2 years, the practical potentialities of streptomycin for disease control were definitely established.

The most spectacular of all the clinical applications followed recognition that streptomycin was highly effective against the tuberculosis organism, not only *in vitro* but also *in vivo*. Several clinical centers undertook to test the sensitivity of different freshly isolated strains of *Mycobacterium tuberculosis* to streptomycin, its practical evaluation in control of tuberculosis in experimental animals, and finally its use in the control of tuberculosis in the human body. Following the lead of Dr. William H. Feldman and Dr. H. Corwin Hinshaw at the Mayo Clinic, the American Trudeau Society and the National Tuberculosis Association took an active part in these investigations. The first conference arranged for the evaluation of the clinical results of the use of streptomycin was held in 1945, and others soon followed.

Within 3 years after the announcement of the isolation of streptomycin came the almost complete elucidation of its chemistry, its first derivative (dihydrostreptomycin) was obtained, and the first thousand clinical cases were reported. From a laboratory curiosity, streptomycin production soon grew into a large industry, with a monthly output of more than 25,000 kg in the United States alone, and with many plants being established abroad for its manufacture.

This marked rise in the development of streptomycin was due partly to the fact that the spectacular increase, between 1941 and 1943, in the use of penicillin for disease control suggested the possibility that there were other antibiotics which could be utilized for the treatment of diseases not sensitive to penicillin. It was the knowledge of the great abundance and wide distribution of actinomycetes, which dated back nearly three decades, and the recognition of the marked activity of this group of organisms against other organisms that led me in 1939 to undertake a systematic study of their ability to produce antibiotics. Between 1940 and 1952 we isolated in our laboratories 10 different chemical substances from cultures of different actinomycetes, beginning with *actinomycin* and ending with *candicidin*. Of these, *streptomycin* proved to be by far the most important chemotherapeutic agent.

Production of Antibiotics by Actinomycetes

The isolation of streptomycin was the culminating point of a painstaking search for antimicrobial agents produced by actinomycetes, a group of organisms closely related to the bacteria. This was preceded by long and continuous research, dating back to 1915, on actinomycetes, their occurrence and abundance in nature, their systematic or taxonomic position, their role in soil processes, notably in the decomposition of plant and animal residues and in the formation of humus, and finally their associative and antagonistic effects upon bacteria and fungi. It was finally established that as much as 20 to 50 per cent of all the actinomycetes found in the soil and in other natural substrates had the capacity to inhibit the growth of other microorganisms.

Streptomyces griseus, the organism which comprised the streptomycin-producing strain, was known in our laboratories from the beginning of our work on actinomycetes, although it was not tested at that time for its antibiotic-producing properties. The ability of actinomycetes to exert injurious effects upon bacteria and fungi has been known for many years. Lieske showed in 1921 that certain strains are able to bring about lysis of many bacteria and antagonize their growth. This process is selective in nature: some of the bacteria are affected, and others are not. Other investigators, notably Gratia and Dath and Rosenthal, demonstrated in 1925 that cultures of organisms designated *Streptothrix*, and now known to be actinomycetes, are capable of dissolving living and dead bacterial cells. In 1937 Nakhimovskaia made the first survey of the occurrence of antagonistic actinomycetes in the soil: 80 cultures were isolated, of which 47 were able to repress bacterial growth, but only 27 liberated into the medium substances which had the capacity to inhibit the growth of gram-positive bacteria, but not of gram-negative bacteria or fungi.

When we began our investigation on the production of antibiotics by actinomycetes in 1939, only two preparations were known to possess antimicrobial properties. These were not true antibiotics, or at least were not recognized as such. One was obtained by Gratia and had the capacity to lyse dead typhoid cells and certain living bacteria; it was later designated by Welsch as actinomycetin. The other was believed to be a lysozyme, which had lytic principles, and was studied by Krassilnikov and Koreniako in 1939.

The first true antibiotic to be derived from a culture of an actinomyces was isolated in our department in 1940. The organism, *Actinomyces antibioticus*, yielded a substance which was designated as actinomycin. It was soon crystallized, and its chemical and biological properties were established. This antibiotic proved to be a quinone-like pigment with an approximate molecular formula of $C_{41}H_{56}N_8O_{11}$. It was highly active against various gram-positive bacteria but to a much lesser degree against the gram-negative organisms. It proved to be extremely toxic to experimental animals.

This practical failure was followed by a comprehensive program of screening actinomycetes for their ability to produce different antibiotics. The fact was revealed that these antibiotics vary greatly in their chemical nature, toxicity to animals, and antimicrobial activities. Some were active against bacteria and actinomycetes, but not against fungi; some were largely active against certain bacteria, especially the

gram-positive types, but not, or to only a limited extent, against the gram-negative forms, whereas others were active alike against various gram-positive and gram-negative bacteria. Some had a very narrow spectrum, being active only, or largely, upon one group of organisms, such as the mycobacteria, or only upon certain fungi, such as yeast-like forms, or upon certain viruses, such as the influenza B types; others had a much wider spectrum, being active upon both bacteria and fungi or upon bacteria, rickettsiae, and the larger viruses.

It was further found in our laboratory and in others that one antibiotic, such as actinomycin and streptothricin, could be produced by several different species. Some organisms give rise to different modifications of the same antibiotic, as actinomycin A, B, and C. This is true also of streptomycin, various modifications of which are produced by different species of *Streptomyces*, notably *S. griseus*, *S. bikiniensis*, and *S. griseocerneus* (streptomycin, mannosidostreptomycin, hydroxystreptomycin). Some organisms produce a mixture of different antibiotics, as in the case of different strains of *S. griseus*, which give rise not only to streptomycin, but also to the antifungal agents cycloheximide and candicidin.

Isolation of Streptothricin and Streptomycin

The isolation of actinomycin, the first true antibiotic from a culture of an actinomyces, pointed a way to the formation and isolation, from species belonging to this group of organisms, of other chemical substances possessing antimicrobial properties. A new type of substance, designated *streptothricin*, was soon isolated (in 1942). It showed distinct promise as a chemotherapeutic agent. It was active against both gram-positive and gram-negative bacteria and appeared to be not very toxic to animals. The organism producing it was identical with *Actinomyces lavendulae*, a culture found in the soil 25 years previously. This new substance possessed highly desirable physical, chemical, and antimicrobial properties and gave promise of filling the gap left by penicillin in the treatment of infectious diseases due to gram-negative bacteria. It was a basic compound soluble in water, with an optimum activity at a slight alkalinity. It was active against a number of bacteria, not only *in vitro* but also *in vivo*, as well as against various fungi. It was resistant to heat and to the action of different microorganisms and enzymes. A study of its pharmacology, however, brought out the fact that streptothricin exerted a residual toxic effect upon the animal body; its use in the treatment of infectious diseases was, therefore, limited.

The experience gained in the study of streptothricin made possible effective planning of a more comprehensive study of the production of a definite type of antibiotic by actinomycetes. Particular attention was paid to substances that possessed chemical and biological properties similar to those of streptothricin but that would be less toxic to the animal body. The method of cultivation of the organism, notably the use of submerged cultures; the method of isolation of the active substance, notably its adsorption on charcoal and its removal with dilute acid; the method of evaluation of its microbial properties, notably its activity against gram-negative bacteria, were now well understood. It was, of course, desirable that any new substance possess a spectrum which would be broader than that of streptothricin, that it be particularly active against a greater variety of bacteria which were resistant to penicillin, and, if possible, that it be active against tuberculosis. (Streptothricin was later found also to possess this property.) Less than 6 months after many freshly isolated cultures of actinomycetes were screened, an organism was obtained which appeared to produce the long-looked-for antibiotic.

Since actinomycin was named after the organism that gave the name to the group of *Actinomycetales* (*Actinomyces* by Harz in 1877), and, since the first promising antibiotic, streptothricin, was derived from the first member of this group to be named (*Streptothrix* by F. Cohn in 1872), it was logical that the first chemotherapeutically active substance should be designated by the newly coined generic name of actinomycetes (*Streptomyces* by Waksman and Henrici in 1943). Thus *streptomycin* was born.

The organism producing streptomycin was identical with a culture isolated in our laboratory in 1916 and described at that time as *Actinomyces griseus* (changed, according to the 1943 classification, to *Streptomyces griseus*). Although numerous additional cultures of streptomycin-producing strains of *S. griseus* have since been isolated, one of the 1943 cultures has been utilized for the commercial production of streptomycin all over the world.

In addition to streptomycin, *S. griseus* was later found to produce mannosidostreptomycin, as well as certain other antibiotics, such as cycloheximide and streptocin. Other strains of this organism produce no antibiotics at all or are able to form other substances, such as grisein and candicidin.

The medium used for the production of streptomycin contained organic sources of nitrogen and carbon, mineral salts, and certain growth-promoting substances. The culture had to be well aerated and incubated at 25–30° C for 3 to 5 days. The activity of streptomycin reached 100–200 μg/ml; in commercial production, much higher yields are usually obtained.

Recovery of the streptomycin was accomplished in a series of operations involving removal of the mycelium by filtration, adsorption of the streptomycin on activated carbon or on some other absorbent, elution by dilute acid, neutralization of the eluate, concentration by evaporation and dehydration or by solvent precipitation, and filtration and drying. Various methods have been used for further purification and crystallization of the antibiotic.

Streptomycin was found to be soluble in water and insoluble in organic solvents, such as ether, chloro-

form, and acetone. The chloride was completely soluble in methanol, less soluble in ethanol, and virtually insoluble in butyl alcohol, acetic acid, and pyridine. The sulfate was only slightly soluble in methanol and virtually insoluble in the other solvents.

A unit of streptomycin was designated as that amount of material which was just sufficient to inhibit the growth of a standard strain of *E. coli* in 1 ml of culture medium. When streptomycin was later isolated in a crystalline state, it was found that 1 unit was comparable to 1 μg of the pure base. The United States Food and Drug Administration, in consultation with the different manufacturers, decided to establish the potency of streptomycin on the basis of the weight of the active material.

The activity of streptomycin against sensitive organisms was found to be influenced by the presence of certain chemical compounds. Glucose reduced its activity appreciably; hydroxylamine, thioglycollate, and cysteine largely inactivated it. This phenomenon was utilized in testing for sterility of streptomycin preparations or for determining the admixture of other antibiotics. The activity of streptomycin was found to be influenced but little by body fluids, pus, or normal tissue juices. The optimum reaction was pH 8.0; increasing acidity resulted in a decreased bacteriostatic potency, the greatest reduction taking place between pH 6.6 and pH 5.9.

Chemical Nature of Streptomycin

Streptomycin belongs to the glucosides in which a diguanido group is linked to a nitrogen-containing disaccharide-like compound. It is a strong base with three basic functional groups. The molecular weight determination on the trihydrochloride in water gave about 800 for the free base after the necessary corrections for the chloride ion.

Upon hydrolysis, streptomycin splits into two compounds:

$$\underset{\text{Streptomycin}}{C_{21}H_{39}N_7O_{12}} + H_2O \longrightarrow \underset{\text{Streptidine}}{C_8H_{18}N_6O_4} + \underset{\text{Streptobiosamine}}{C_{13}H_{27}NO_9}$$

On further hydrolysis with strong mineral acids, the streptobiosamine gives a 6-carbon sugar and glucosamine:

$$\underset{\text{Streptobiosamine}}{C_{13}H_{27}NO_9} + H_2O \longrightarrow \underset{\text{Streptose}}{C_6H_{10}O_5} + \underset{\text{N-Methyl-1-glucosamine}}{C_7H_{15}NO_5}$$

The basic nitrogen atom in the streptobiosamine is not present as a primary amino group.

The structure of the streptomycin molecule is usually given as in Fig. 2.

Antibacterial Properties of Streptomycin

Streptomycin is active against a large number of bacteria found among the gram-negative, gram-positive, and acid-fast groups and among the spirochetes; it has relatively little activity against anaerobic bacteria, fungi, protozoa, and viruses. No absolute value

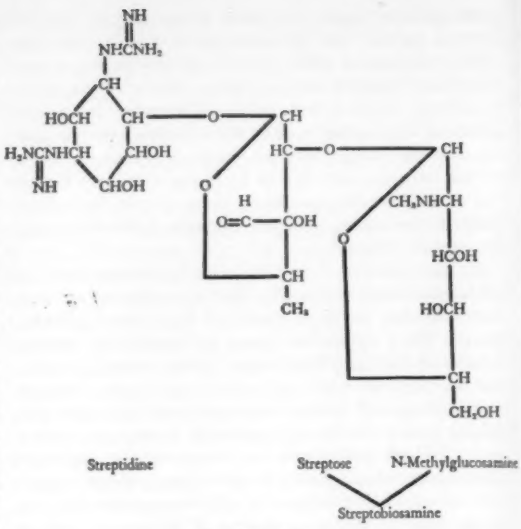

Fig. 2.

can be given for the sensitivity of an organism to streptomycin; this depends not only upon the particular species, but also upon the strain of the organism and upon the composition of the medium in which it is tested. Thus, any given figure for a single organism is quite arbitrary, since such values can vary greatly.

Streptomycin is more active upon bacteria in young, actively growing cultures than upon bacteria in older cultures, although this difference does not appear to be so great as that for penicillin. When added to a 3-hour-old culture of *E. coli*, 2 μg of streptomycin reduced the numbers by 75 per cent, and 5 μg by 95 per cent; the corresponding reductions for 24- to 48-hour-old cultures were 19 and 42 per cent. The size of the inoculum influences the bacteriostatic concentration of streptomycin: for instance, an inoculum of 30,000 cells of *Brucella abortus* required 1 μg/ml for inhibition of growth, whereas an inoculum of 30,000,000 cells required 4 μg/ml. Less streptomycin was needed to inhibit growth of various strains of *Br. abortus* and *Br. suis* under aerobic conditions than in the presence of 10% CO_2.

Since streptomycin is not active against viruses, it can be utilized in their isolation and purification from bacterial infections. It is also used in the preservation of bull semen, in the purification of cultures of *Trichomonas vaginalis* and *T. foetus*, and in the development of media for the isolation of pathogenic fungi. Because of its marked antibacterial properties, streptomycin can be used in preventing wound infections and in surgical operations.

Among the antimicrobial properties of streptomycin, its bacteriostatic and bactericidal action upon different strains of *Mycobacterium tuberculosis* is particularly significant. In a concentration of 0.05 μg/ml, it has been found capable of inhibiting growth

of the human pathogen to a limited extent; 0.2 μg/ml inhibits growth to a marked extent; and 0.4 μg/ml stops growth completely, after an incubation time of 16–20 days. In other experiments, streptomycin gave complete inhibition of growth of *M. tuberculosis* in concentrations of 0.3 μg/ml, although occasional colonies occurred even with 0.5 μg/ml. The bactericidal action of streptomycin also varies with its concentration, and the length of contact with the organism, 0.3 μg/ml exerting a marked effect in 48 hr, and 20 μg/ml in 6 hr.

Resistance of Bacteria to Streptomycin

The problem of variation in sensitivity of different strains of the same organism to streptomycin and the increasing resistance of the bacteria on prolonged contact with it are of considerable theoretical and practical importance. Variation in sensitivity may differ from day to day. This is believed to be due, at least in part, to variations in the number of viable organisms, age and density of the culture, and the particular species involved.

Freshly isolated cultures of tubercle bacilli from patients with pulmonary tuberculosis are uniformly sensitive to streptomycin. The organism develops resistance to streptomycin *in vitro* at a rapid rate, and this resistance persists for a considerable time; it is not accompanied by any diminution in virulence. In a growing culture of tubercle bacilli, there was found to be, however, a decrease in the proportion of streptomycin-resistant cells with an increase in the age of the culture. The principal effects of streptomycin on the morphology of the organism were a loss of acid-fastness, an increase in granulation, and, in highly bacteriostatic concentrations, a shortening of the rods.

Successive transfers of bacteria commonly occurring in infections of the urinary tract resulted in an increase in resistance to more than 1000 μg/ml of streptomycin. After 29 subsequent daily transfers on common media, the bacteria lost none of their resistance. It was suggested, therefore, that streptomycin-fastness may be a major factor in the failure of streptomycin therapy in certain infections. When the disease condition presents physical barriers to the penetration of the streptomycin, as in abscesses and pyelonephritis, the organisms are exposed to sublethal concentrations, thus resulting in increased resistance. In infections with *Aerobacter cloacae*, an increase of more than 1000 times was obtained after 36 days of treatment.

Streptomycin in Experimental Infections

Streptomycin proved highly effective in the treatment of a large number of infectious diseases brought about in experimental animals by various bacteria. This was true of *Salmonella schottmülleri, Shigella gallinarum, Brucella abortus, Pseudomonas aeruginosa, Klebsiella* or Friedländer's bacillus, *Diplococcus pneumoniae*, and a number of organisms commonly found in urinary tract infections.

Subcutaneous doses of 100–200 μg of streptomycin were sufficient to protect mice against lethal infections with *S. schottmülleri*. Oral doses of about 3 mg were required to protect mice infected by the intraperitoneal injection of 10 lethal doses. After oral administration, streptomycin remained in the intestinal tract and gave very low blood concentrations. Recovery of streptomycin from the urine of the animals ranged from 70 to 80 per cent when streptomycin was given parenterally but was less than 10 per cent when given orally.

The effectiveness of streptomycin against tularemin, caused by *Pasteurella tularensis*, has been most striking. Complete protection was also obtained in experimental infections due to *Proteus vulgaris*: in chick embryos, 1000 μg of streptomycin were required to arrest 18-hr infections; to protect 50 per cent of the embryos, 250 μg in a single dose or 150 μg in three daily doses were required. Excellent protection was obtained by the use of 150 μg of streptomycin against fowl typhoid caused by *Sh. gallinarum* in 11-day-old chick embryos.

Streptomycin was also found to have a marked effect upon experimental plague, *Pasteurella pestis* being inhibited by 1 μg/ml. A series of mice infected with the organism were treated with 400 μg of streptomycin daily, beginning 2 days after inoculation and continuing for 6 days. Nine of the 10 mice survived 14 days, as compared with the survival of 4 out of 11 for sulfadiazine-treated mice and 1 out of 9 for the controls. Experimental infections caused by *Diplococcus pneumoniae* and *Staphylococcus aureus* were readily controlled when adequate doses of streptomycin were employed.

Of particular importance was pioneering work done by Feldman and Hinshaw on the effectiveness of streptomycin in experimental tuberculosis in guinea pigs. On the basis of an arbitrarily established index of infection, microscopically determined, 100 represented the maximum possible amount of tuberculosis. The control animals, sacrificed after 61 days, exhibited an index of 67 as contrasted to 5.8 for those which had received streptomycin. In another experiment, the corresponding values were 81.9 for the untreated and 2.8 for the treated animals. The daily administration of streptomycin per guinea pig varied from 1387 to 6000 μg. Two different strains of the human tubercle bacillus were equally sensitive to streptomycin. *M. tuberculosis* was recovered from the spleen of only one of the guinea pigs treated with streptomycin, the animal having received 1387 μg of streptomycin daily for 54 days.

The conclusion was reached that streptomycin is the most effective tuberculo-chemotherapeutic agent so far studied. Its relatively low toxicity for guinea pigs, its high efficacy in resolving and suppressing what would otherwise be lethal tuberculosis, established streptomycin as a drug worthy of serious consideration for the treatment of tuberculosis.

Toxicity of Streptomycin

To produce toxic manifestations of streptomycin in animals, it was necessary to administer either extraordinarily large doses of the pure material or smaller amounts of certain impure preparations. No correlation was obtained between the acute toxicity of different lots to experimental animals and clinical tolerance by human beings. The behavior of the material in man could not, therefore, be foretold if antibacterial potency alone was assumed to be the criterion of purity; highly concentrated material had on occasion been unsatisfactory clinically, whereas considerably less active preparations had often produced no undesirable effects.

Among the various toxic reactions resulting from the administration of streptomycin, the otic complications received particular attention. In one experiment, 81 patients treated with streptomycin were examined for evidence of aural toxicity. Two months after cessation of therapy, 3 of these patients showed an absence of vestibular response. During the third month after therapy, 1 of these 3 showed increasing recovery of response. All three complained spontaneously of dizziness, which decreased steadily during treatment. One patient showed a high tone loss, but the audiogram was normal in these three patients. Another patient showed a severe loss of hearing 2 weeks after treatment; 2 weeks later he had shown decided improvement in hearing; he had a normal vestibular response throughout. It was not certain that the low tone and high tone losses were due to streptomycin.

Diseases Responding to Streptomycin

A variety of human and animal diseases caused by various bacteria respond readily to streptomycin treatment. This was brought out in the first comprehensive study of a group of diseases which could be considered to be definitely controlled by streptomycin or to give promise that they would respond favorably. These included tularemia, urinary tract infections, especially those resistant to sulfa drugs and to penicillin, *Klebsiella* and *Hemophilus* infections, bacteremia due to penicillin-resistant organisms, various forms of meningitis, and whooping cough. Streptomycin was also found helpful in treatment of a variety of other diseases, such as leprosy, brucellosis, certain forms of tuberculosis, and probably also bacillary dysentery, cholera, and bubonic plague.

The Committee on Chemotherapy, originally organized by the Committee on Medical Research of the OSRD, undertook the supervision and coordination of the first large-scale series of investigations of the use of streptomycin in the treatment of bacterial infections. The various infectious diseases have been divided, in their relation to streptomycin, as follows:

Diseases Definitely Indicated for Streptomycin Treatment

1. All cases of tularemia.
2. All cases of *H. influenzae* infections:
   - Meningitis
   - Endocarditis
   - Laryngotracheitis
   - Urinary tract infections
   - Pulmonary infections
3. All cases of meningitis due to:
   - *E. coli*
   - *Pr. vulgaris*
   - *K. pneumoniae*
   - *B. lactis-aerogenes*
   - *Ps. aeruginosa*
   - *S. paratyphi*
4. All cases of bacteremia due to gram-negative organisms:
   - *E. coli*
   - *Pr. vulgaris*
   - *A. aerogenes*
   - *Ps. aeruginosa*
   - *K. pneumoniae*
5. Urinary tract infections due to:
   - *E. coli*
   - *Pr. vulgaris*
   - *K. pneumoniae*
   - *B. lactis-aerogenes*
   - *H. influenzae*
   - *Ps. aeruginosa*

Streptomycin Found to be a Helpful Agent but Position not yet Definitely Defined

1. Peritonitis due to gram-negative bacilli.
2. B. Friedländer's pneumonia.
3. Liver abscesses due to gram-negative bacilli.
4. Cholangitis due to gram-negative bacilli.
5. Penicillin-resistant but streptomycin-sensitive organisms infecting heart valves.
6. Tuberculosis.
7. Chronic pulmonary infections due to mixed gram-negative flora.
8. Empyema due to gram-negative infections.

The Committee evaluated the first thousand cases treated with streptomycin. In 409 urinary tract infections, the general recovery rate was 42 per cent. Of 100 *H. influenzae* meningitis infections, recovery was obtained in 79 per cent; in 17 of the fatal cases, treatment was too late to be effective. In 14 cases of meningitis caused by other gram-negative organisms, only 4 patients died. In 91 bacteremia cases, 49 patients recovered, 12 improved, 4 showed no response, and 26 died; in this group as well, the fatal cases were treated too late. Striking results were obtained in tularemia (63 recoveries out of 67 cases) and in otitis media (7 immediate recoveries out of 8 cases). In 44 cases of pulmonary infections, recovery or improvement was obtained in 61 per cent. Streptomycin was extremely effective against acute Friedländer bacillus infections.

In the evaluation of streptomycin in tuberculosis, 75 cases were used. These included miliary, meningeal, larynx, skin, and renal tract forms. It was recommended that a minimum period of treatment should be 3–6 months, with daily doses of 1.5 to 3.0 g. Hinshaw, Feldman, and Pfuetze, on the basis of treatment of 100 tuberculosis cases, came to the rather optimistic conclusion that streptomycin was an antibacterial

agent which possesses the unique ability to inhibit the growth of *M. tuberculosis* both experimentally and clinically. It was recommended that treatment of tuberculosis consist of large doses of streptomycin for prolonged periods.

Various forms of tuberculosis were soon found to respond promptly to streptomycin. These included ulcerating tuberculous lesions of the larynx, hypopharynx, and the tracheobronchial tree, which received combined intramuscular and aerosol treatment. Some types of extrapulmonary tuberculosis also responded well, especially chronic, long-standing draining sinus tracts, which usually closed within a few weeks. These remained closed only if treatment was continued for several weeks after superficial healing. Encouraging results were also obtained in treatment of tuberculosis of bones and joints. Some patients with early tuberculous meningitis responded promptly to adequate intramuscular and intrathecal administration, but frequently these gains were not permanently sustained; temporary clinical remission was frequently realized after streptomycin treatment of early but acute and severe tuberculous meningitis; consciousness could be regained, sometimes within a few days, fever would decline within a few weeks, the patient appearing normal for several months; subsequent exacerbations of the diseases were likely to occur and were not likely to respond to treatment.

Disseminated hematogenous tuberculosis of the miliary type heretofore did not respond to treatment, spontaneous recoveries being extremely rare. By the use of streptomycin, it was possible to bring about a complete clinical and roentgenologic remission. Tuberculosis of the alimentary tract and tuberculous peritonitis also showed striking symptomatic improvement.

The rapid progress made in the use of streptomycin in tuberculosis was well described by Walker, Hinshaw, and Barnwall: "The introduction of streptomycin into clinical medicine has been peculiarly exciting to phthisiologists. Not only have they never had an 'antibiotic' which was helpful in the treatment of tuberculosis in man, they have never had a proved effective drug of any sort. So far as chemotherapy is concerned, not only was their situation comparable to that of the syphilologist prior to the discovery of penicillin, it was worse than his position before the appearance of Ehrlich and arsenic. Phthisiologists have been dependent on rest in bed, and, more recently, on collapse therapy. The relatively rapid evaluation of a new drug—rapid for tuberculosis if not for pneumococcic pneumonia—is partly the result of experience gained from the investigation of other drugs in other diseases. It is partly a result of the employment, here and in England, of cooperative methods of investigation which have yielded data, reasonably uniform, rapidly, and in large amount."

I need hardly survey the subsequent developments in the use of streptomycin for the different infectious diseases, especially tuberculosis. I need hardly dwell upon the various regimens for treatment, based on special dosages and modes of administration, and the use of streptomycin in combination with *p*-aminosalicylic acid (PAS). I need not list the numerous antibiotics that have been isolated from cultures of actinomycetes, some in our own laboratories, such as neomycin, and some in numerous other laboratories throughout the world. Suffice to say that streptomycin pointed the way, both through the planned screening programs and through its specific activity against the gram-negative bacteria and tuberculosis, to many of these antibiotics. The rest is history. Medical science and clinical practice have been revolutionized. One may look forward to further discoveries of agents that will combat diseases not now subject to therapy, to more active and less toxic agents than those now available, and to combined therapy of several antibiotics or of antibiotics and synthetic compounds which will prove more effective than the use of single substances.

The discovery of streptomycin as a product of a rather obscure group of microorganisms, the actinomycetes, led to the study of these organisms as potential producers of other chemotherapeutic substances. After streptomycin, there came in rapid succession chloramphenicol, aureomycin, neomycin, terramycin, and, more recently, erythromycin and others. These antibiotics have found extensive application as chemotherapeutic agents in the treatment of numerous infectious diseases never before subjected to therapy.

In the treatment of tuberculosis, the more controlled dosage of streptomycin and the supplementary use of PAS tended to overcome some of the limitations of the antibiotic, notably its toxicity and the development of bacterial resistance. The recent introduction of isonicotinic acid hydrazide suggests the possibility that its use in combination with streptomycin will tend further to control the disease and overcome undesirable complications. The conquest of the "Great White Plague," undreamt of less than 10 years ago, is now virtually within sight.

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News and Notes

National Conference on Weights and Measures

ATTENDANCE at the Thirty-Eighth National Conference of Weights and Measures, May 19–22, 1953, exceeded that of all such previous meetings, both in total number of delegates and number of states represented. The 430 delegates represented many cities and counties, the federal government, manufacturers, railroads, business, industry, and trade associations, in addition to 39 states and the District of Columbia.

The Conference, sponsored by the National Bureau of Standards, met in Washington, D. C. The function of the Bureau in the field of standardizations of weights and measures and their administration is advisory only. The federal government has no regulatory authority in this field, which is entirely the responsibility of state and local governments.

Actions by the Conference are recommended to the states for official promulgation. The Thirty-Eighth National Conference adopted a Model Regulation on Package Marking Requirements, patterned after the Federal Food, Drug, and Cosmetic Act, as well as recommended methods of sale of anhydrous ammonia and other liquid chemical fertilizers with pressure characteristics; preheated fuel oils; peat moss in package form; rope; seeds (agricultural, horticultural, floricultural); and pickles and pickle products in package form.

A tentative code for farm milk tanks offered by the Conference Committee on Specifications and Tolerances was adopted, as were minor amendments to the scale code.

These codes and amendments are incorporated into National Bureau of Standards Handbook 44, *Specifications, Tolerances, and Regulations for Commercial Weighing and Measuring Devices*, and are recommended by NBS for official adoption by the states. During the Conference it was announced that 26 states had officially adopted the Handbook 44 codes and that many other states are applying the provisions of the codes in their enforcement procedures.

The Conference unanimously adopted a resolution of appreciation to and confidence in its president, Dr. A. V. Astin, National Bureau of Standards Director. Another resolution expressed appreciation of the Bureau's services and sponsorship of the Conference.

Dr. Astin was re-elected President of the Conference. Six vice-presidents were elected: G. F. Austin, Jr. (Detroit, Michigan); J. E. Boyle (Maine); F. M. Green (Connecticut); J. R. Jones (South Carolina); J. W. Reese (Iowa); and A. C. Samenfink (Rochester, New York). W. S. Bussey (NBS Office of Weights and Measures) was re-elected Secretary, and J. P. McBride (Massachusetts) was elected Treasurer.

Scientists in the News

Postmaster General Summerfield on August 13 cancelled his fraud order against the battery additive AD-X2. On the following day Secretary of Commerce Weeks reinstated **Allen V. Astin** as Director of the National Bureau of Standards. Dr. Astin's suspension in April was based on the Bureau's report on AD-X2. The committees appointed by Secretary Weeks to provide guidance on the organization of the NBS and on the effective character of AD-X2 have not as yet submitted their reports. These have been promised for public release.

Samuel L. Meyer, Executive Director of the American Institute of Biological Sciences and Executive Secretary of the Division of Biology and Agriculture of the National Research Council since September 1, 1952, returned at the termination of his year's leave of absence to Florida State University, Tallahassee, where he is Professor and Head of the Department

of Botany. During his term of office, Dr. Meyer has done much to further the interests of A.I.B.S. societies and has set in motion many projects that will benefit biologists in the years ahead. He is succeeded by **Frank L. Campbell,** entomologist, who was editor of THE SCIENTIFIC MONTHLY from 1943 to 1948, and who since then has been a collaborator in the U.S. Department of Agriculture. Dr. Campbell has a broad background of experience in biological teaching, research, publication, and administration.

H. Burr Steinbach, Professor of Zoology at the University of Minnesota, and **Raymond H. Ewell,** Manager of the Chemical Economics Service, Stanford Research Institute, have been appointed to the staff of the National Science Foundation. As Assistant Director for Biological and Medical Sciences, Dr. Steinbach will direct activities in support of basic research and the correlation of Federal research in these fields. He replaces **Fernandus Payne,** who has served the Foundation for the past year and who now plans to return to his research at Indiana University. Dr. Ewell has been named Assistant Director for Program Analysis, in which post he will be responsible for conducting a series of Foundation studies on the status of research in industry, the universities, and government, with particular emphasis on the extent of Federal participation in research and development activities of the nation. He will also be concerned with the relationship between research and industrial development, and other questions relating to the effects of research on the nation's economy and health.

Frank L. Stillwell, internationally known Australian geologist, has retired from his position as Officer-in-Charge of the Commonwealth Scientific and Industrial Research Organization, Mineragraphic Section.

Lewis L. Strauss, New York financier and rear admiral in the U.S. Naval Reserve, has succeeded Gordon Dean (News and Notes, July 24) as Chairman of the Atomic Energy Commission. Admiral Strauss was named a member of the Commission when it was established in 1946 and served until 1950 when he resigned to return to his private interests. President Eisenhower brought him back to the government in March of this year as a special assistant to the President, a "liaison adviser on atomic energy matters."

Raymond L. Taylor, Associate Administrative Secretary, AAAS, has been elected a member of the Board of Trustees of *Biological Abstracts* as the representative of the Association.

Ira Rockwood Telford, formerly chief of the Anatomy Department, University of Texas School of Dentistry, Houston, has returned to George Washington University School of Medicine, Washington, D. C., as professor and executive officer of its Department of Anatomy. He left his post there in 1947 to go to Texas. Dr. Telford replaces **Warren Andrew,** who resigned last year to join the Bowman Gray Medical School faculty at Winston-Salem, N. C.

Edward L. Turner, Dean of the School of Medicine at the University of Washington since 1945, has been appointed Secretary of the American Medical Association's Council on Medical Education and Hospitals, effective Oct. 1.

Ralph W. Tyler, Dean of the Division of Social Sciences at the University of Chicago, has been appointed Director of the Ford Foundation's recently established Center for Advanced Study in the Behavioral Sciences. As executive head of the Center, the site for which has yet to be selected, Dr. Tyler will administer a study program in human relations. The Foundation has appropriated $3,500,000 to cover the cost of the project for 6 years. The funds will be used mainly to permit 50 scholars and scientists to assemble at the Center each year for study and training.

James H. Wiegand, formerly Associate Head of the Rockets Department at the Naval Ordnance Test Station, has been named Assistant Chairman of the Department of Chemistry and Chemical Engineering, Southwest Research Institute, San Antonio, Texas.

Russell M. Wilder has retired as Director of the National Institute of Arthritis and Metabolic Diseases, for reasons of health. An internationally known nutrionist and authority on diabetes, Dr. Wilder became the first director of NIAMD, one of the seven National Institutes of Health, shortly after its creation in 1950. Previously, he was Chief of the Department of Medicine at the Mayo Foundation. Most of his career, from 1919 to 1950, was with the Mayo Foundation and Clinic.

In 1940 Dr. Wilder was Chairman of the Committee on Medicine of the National Research Council, in which he organized the Food and Nutrition Board. He was Chairman of the Board in 1941 and 1942. The following year he served as Chief of the Civilian Food Requirements Branch, War Food Administration, and in 1950 he was a special consultant to the Research Facilities Planning Committee of the National Institutes of Health. For 20 years (1930–1950) he was a member of the American Medical Association's Council on Foods, and will be remembered for his part in bringing about the general acceptance and use of enriched white flour and bread. Dr. Wilder is the author of two medical textbooks and numerous research reports.

George Zur Williams, Director of Cancer Research at the Medical College of Virginia, has been granted a leave of absence for one year to organize a department of clinical pathology for the National Institutes of Health. During the year he will continue his fundamental studies in cancer as an associate in the National Cancer Institute. **Louis A. Leone** will act as departmental head in Dr. Williams' absence.

Julius Lane Wilson has been appointed to the newly created post of Director of Medical Education of the Medical Section of the National Tuberculosis Association, New York City. For the past year Dr. Wilson has been Director of Clinics and Professor of Medicine in the Henry Phipps Institute, University of Pennsylvania, and chief consultant to the Bureau of Tuberculosis Control, Pennsylvania Department of Health. He will continue to devote part of his time to his work in Philadelphia.

George W. Wright has resigned as Head of the Physiology Department, Trudeau Foundation, Saranac Lake, N. Y., to accept a position as St. Luke's Hospital, Cleveland, directing a department of research. His successor will be **Giles F. Filley,** who has been associated with Dr. Wright at Trudeau since 1947.

Capt. O. D. Yarbough, MC, USN, a submarine officer, has been named Director of the Research Division, Bureau of Medicine and Surgery, Department of the Navy, Washington, D. C.

Education

The **American Board of Nutrition** will hold certifying examinations in Atlantic City during April, 1954. Completed applications of persons wishing to be considered for certification should be in the office of the Secretary *not later than February 1, 1954.* Application forms may be obtained from the Secretary, Otto A. Bessey, Dept. of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Tex.

A new program in social psychology, leading to the Ph.D. degree, has been announced by **Columbia University.** Selected members of the departments of Psychology, Sociology, Anthropology, and Education comprise a guiding committee under the auspices of the University's Joint Committee on Graduate Instruction. Course offerings for the new program have been drawn from the fields of psychology, sociology, anthropology, political science, communication, industrial engineering, and group work, supplementing general and specialized courses in social psychology. Admission to the program will be limited to 12 students beginning their graduate study and 12 advanced students. Application may be made to Prof. Goodwin Watson, Teachers College, Columbia University, New York 27, N. Y.

Twenty-three training courses in various aspects of environmental sanitation will be conducted by the **Environmental Health Center** of the Public Health Service at Cincinnati during the period July 1, 1953, to June 30, 1954. These short courses are given for professional personnel from State and local health departments, water pollution control agencies, the Public Health Service, other governmental units, educational institutions, and industries cooperating with these agencies in environmental sanitation programs. Detailed information is available upon request from the Officer in Charge, Environmental Health Center, Public Health Service, Dept. of Health, Education, and Welfare, Cincinnati, Ohio.

The **Illinois Institute of Technology** and the **Machinery and Allied Products Institute** are jointly sponsoring the new National Center of Education and Research in Dynamic Equipment Policy which will be established this fall at I.I.T. The Center will seek to help industry solve its problems and improve its practices in the field of capital equipment acquisition and replacement.

Radiation safety will be outlined in a course to be given by the Department of Industrial Medicine of the **New York University Post-Graduate Medical School** in cooperation with the U.S. Atomic Energy Commission and the NYU College of Engineering. Designed to acquaint present and potential users of radioisotopes and X-ray equipment with safety precautions, the course will be given once a week for 15 weeks at the Institute of Industrial Medicine, beginning Sept. 23. Detailed information may be obtained from the Office of the Dean, New York University Post-Graduate Medical School, 477 First Ave., New York 16, N. Y.

The Institute of Applied Arts and Sciences of the **State University of New York** has been renamed Mohawk Valley Technical Institute.

The Department of Psychology and the Division of Biological Sciences of the **University of Chicago** have announced the establishment of a Section of Biopsychology which will supervise a graduate training program for the Ph.D. degree in the general area of a biologically oriented psychology. The program, leading to the Ph.D. degree in biopsychology, will normally occupy three years of full-time study and research. One-third of this time will be devoted to psychology, with concentration on the subject matter of areas known in the past as physiological, comparative, and general experimental psychology. The student will have one-third of his time available for elective courses and seminars from such related departments as Anatomy, Biochemistry, Biophysics, Mathematics, Medicine, Physiology, and Zoology. The remaining third of his time will be spent on laboratory research which will be begun during the first year of study and continued throughout the program. Formal instruction in biopsychology will commence in the Autumn Quarter of 1953. Detailed information can be obtained from Prof. Ward C. Halstead, Chairman of Biopsychology, University of Chicago, Chicago, Ill.

A 12-month course for laboratory aides, a pioneer venture by the General Extension Division and the College of Medical Sciences, will begin Sept. 28 at the **University of Minnesota.** Geared to prepare young men and women for work as laboratory assistants to medical technologists and physicians, the course will

include six months of classes on the University campus and six months of practical training in local hospital laboratories. The course will be run in conformity with the requirements for certification of laboratory aide under the Registry of Medical Technologists of the American Society of Clinical Pathologists. Further information can be obtained from the Medical Technology Office, W225, University Hospitals, University of Minnesota, Minneapolis 14.

Grants and Fellowships

The **American Heart Association** has announced that entries are now being received for the second annual Howard W. Blakeslee Award of $1,000 for outstanding scientific reporting in the field of heart and blood vessel diseases. The award will be presented to the individual whose creative efforts during 1953 in any medium of mass communication—including newspapers, magazines, radio, television, films, or books—are judged to have contributed most to public understanding of heart and circulatory diseases. Material published or produced during the 1953 calendar year is eligible for consideration. Entries must be postmarked *not later than January 15, 1954.* The winner will be announced at the Annual Meeting of the American Heart Association, to be held in April, 1954, in Chicago. Entry blanks and additional information may be obtained from the Chairman, Managing Committee, Howard W. Blakeslee Award, American Heart Association, 44 E. 23 St., New York 10, N. Y.

The **Arthritis and Rheumatism Foundation** is offering the following research fellowships in the basic sciences related to arthritis:

1. Predoctoral fellowships ranging from $1,500 to $3,000 per annum, depending on the family responsibilities of the fellow, tenable for 1 year with prospect of renewal.

2. Postdoctoral fellowships ranging from $3,000 to $6,000 per annum, depending on family responsibilities, tenable for 1 year with prospect of renewal.

3. Senior fellowships for experienced investigation will carry an award of $6,000 to $7,500 per annum and are tenable for 5 years.

The *deadline for applications is November 1, 1953.* Applications will be reviewed and awards made by February 15, 1954. Detailed information and application forms may be obtained from the Medical Director, The Arthritis and Rheumatism Foundation, 23 W. 45 St., New York 36, N.Y.

Applications for grants from the **James Picker Foundation for Radiological Research,** headed by Mutual Security Director Harold E. Stassen, may now be submitted for next year. In the past three years, funds totalling $80,000 have been made available to mature investigators to further broaden the uses of radiology. Awards of grants, fellowships, and scholarships are given in support of a specific research program under the direction of a responsible investigator. Any project offering promise of improvement or development in radiological methods of diagnoses or treatment of disease is eligible for assistance from the Picker Foundation.

Qualified applications from any country in the world may be submitted with their proposed study in outline form. *Final applications should be submitted no later than November 30, 1953.* Applications for grants-in-aid and fellowships should be directed to: James Picker Foundation, Inc., Hanover Bank Trustee, 70 Broadway, New York 4, N. Y., or Secretary, Division of Medical Science, National Research Council, 2101 Constitution Ave., N.W., Washington 25, D. C.

The first of a series of studies designed to explore in detail the impact which a "saturation" health insurance program would have on an entire county has been launched by **Mississippi State College** and the **Health Information Foundation** under a Health Information Foundation grant of $39,000. The project is part of an over-all $310,000 Foundation research program to study voluntary health insurance plans in the United States.

The **Muscular Dystrophy Associations of America, Inc.** have approved the following new grants:

Columbia University, $12,474 for 1 year commencing Oct. 1. Principal Investigator, David Nachmansohn.

University of Rochester, School of Medicine and Dentistry, $16,135 for 1 year commencing July 1. Principal Investigator, Karl E. Mason.

National Institute of Neurological Diseases and Blindness, continuation of last year's studies at annual rate of $6,858 commencing July 1. Principal Investigator, G. Milton Shy.

In the Laboratories

Foster D. Snell, Inc. of New York, consulting chemists and engineers, have announced the formation of an Engineering Physics Department in the Engineering Division of the firm. Walter L. Hardy, chemical engineer, is Director of Engineering, and Joseph P. McGill, physicist, will be in charge of the Engineering Physics Department. The new department will conduct investigative work on various problems in the physical sciences. One of its primary functions will be to study shock and vibration and their effect on packaged and unpackaged instruments and delicate equipment.

Meetings and Elections

The **American Association of Clinical Chemists** has elected the following officers for 1953–54: president, Hugh J. McDonald, Loyola University, Chicago, Ill.; vice president, Monroe E. Freeman, Army Medical Center, Washington, D.C.; secretary, Max M. Friedman, Lebanon Hospital, New York; treasurer, Louis B. Dotti, St. Luke's Hospital, New York.

The **American Psychosomatic Society** will hold its 11th Annual Meeting at the Jung Hotel in New Or-

leans, March 27–28, 1954. The Program Committee would like to receive titles and abstracts of papers to be considered for the program *by Dec. 1, 1953*. The time allotted for the reading of each paper will be 15–25 minutes. The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ecology. The Program Committee requests that abstracts be submitted in quadruplicate to the Chairman, at 551 Madison Ave., New York 22.

The **American Society of Medical Technologists** has elected the following officers for 1953–54: president, Mary Nix, Portland, Ore.; president-elect, Ruth Hovde, Minneapolis, Minn.; recording secretary, Sister Mary Simeonette, Louisville, Ky.; treasurer, Mary F. Eichman, Philadelphia, Pa.; executive secretary, Rose Matthaei, Houston, Tex.

Miscellaneous

Descriptions of 28 patents owned by the U.S. Government and held by the **Atomic Energy Commission** have been transmitted to the U.S. Patent Office for registry and listing in the official register of patents. The Commission will grant non-exclusive, royalty-free licenses on the listed patents, as part of its program to make non-secret technological information available for use by industry. Commission-held patents and patent applications released for licensing now total 593.

Air Force scientists have developed a new technique for the stabilization of **zirconium dioxide**, a material capable of withstanding temperatures over 4000 degrees Fahrenheit. This high temperature ceramic material will play an important role in future aircraft developments, such as in rockets, turbo-jets, and high temperature metallurgical research. Responsible for this new development are the ceramic research scientists in the Flight Research Laboratory at the Air Research and Development Command's Wright Air Development Center, Dayton, Ohio.

Recent Deaths

Abbott W. Allen (51), medical professor and clinic chief, New York, N. Y. Aug. 1; **Roy Philip Ash** (46), biologist, Richmond, Va., July 21; **George Bennett** (79), civil engineer, New Milford, Conn., Aug. 11; **Guido Bergamo** (59), physician and radiologist, Venice, Italy, June 26; **William Berry** (69), physiological psychologist, Washington, D. C., July 11; **Isra Broadwin** (60), psychiatrist, London, Eng., Aug. 5; **Jacques Jacob Bronfenbrenner** (69), immunologist, Winston-Salem, N. C., Aug. 13; **Robert B. J. Brunn** (42), electronics engineer, Grand Forks, N. D., July 30; **Willoughby M. Cady** (46), physicist, Pasadena, Calif., June 29; **George H. Chadwick** (76), geologist, Selkirk, N. Y., Aug. 15; **George I. Christie** (72), president emeritus of Ontario Agricultural College, Guelph, Ontario, Aug. 3; **Oswald Dale** (71), electrical insulation engineer and inventor, Nutley, N. Y., July 21; **Albertus De Friest** (64), civil engineer, Los Angeles, Calif., July 26; **William A. Dudley** (57), equipment research engineer, New York, N. Y., Aug. 17; **Abraham P. Friesen** (66), physicist, Austin, Tex., July 31; **Anton Frolov-Bagreyev** (75), agriculturist, Moscow, Russia, Aug. 16; **C. Justus Garrahan** (44), electrical engineer, Swarthmore, Pa., Aug. 10; **Newell Clark Gilbert** (72), professor of medicine emeritus, Milwaukee, Wis., Aug. 1; **Donald Gordon** (73), surgeon, Buffalo, N. Y., Aug 14; **Mervyn H. Gordon** (81), bacteriologist, London, Eng., July 28; **Newell T. Gordon** (63), physical chemist, Albany, N. Y., July 18; **Henry S. Guterman** (37), endocrinologist, Chicago, Ill., Aug. 6; **J. Samuel Guy** (69), chemistry professor, Atlanta, Ga., Aug. 16.

John Howe Hall (72), metallurgical engineer, Tarrytown, N. Y., Aug. 4; **Elmer L. Henderson** (68), past president of AMA and WMO, Louisville, Ky., July 30; **C. Leonard Huskins** (55), professor of botany, Madison, Wis., July 26; **Harriet Hyde** (78), physician and co-founder of Greenwich Hospital, Greenwich, Conn., Aug. 15; **Oscar W. Irvin** (64), mathematician and professor, New York, N. Y., July 23; **Alphons O. Jaeger** (66), chemist, Waldorf, Md., July 22; **Doyle Joslin** (58), surgical research associate, Toronto, Canada, Aug. 18; **Reginald C. Lamb** (60), mathematician, Annapolis, Md., July 22; **Bertram A. Lenfest** (86), metal work expert, Brooklyn, N. Y., Aug. 5; **Guenzter Loeser** (40), scientist, O'Neill, Nebr., July 30; **Nathan T. Milliken** (47), medical professor and internist, Hanover, N. H., Aug. 9; **Mary Elizabeth Morse** (75), medical author, Baltimore, Md., Aug. 1; **Arthur Mulder** (57), physiologist and heart disease expert, Chicago, Ill., Aug. 13; **Frances Park** (72), educator and psychoanalyst, Boston, Mass., July 21; **P. J. Parrott** (79), entomologist, Geneva, N. Y., Aug. 10; **Eugene Paton**, scientist, Kiev, Russia, Aug. 12; **Daniel E. Phillips** (88), mathematician and psychologist, Grand Junction, Colo., July 24; **William C. Pritchard** (71), professor of embryology and histology, Philadelphia, Pa., Aug. 3.

Erskine Ramsay (88), mining engineer and inventor, Birmingham, Ala., Aug. 15; **Arthur P. Saunders** (84), chemistry professor, Clinton, N. Y., Aug. 14; **Jorgen Nilsen Schaumann** (74), dermatologist, Stockholm, Sweden, Aug. 10; **Hugh E. Setterfield**, anatomist, Columbus, Ohio, March 16; **Samuel B. Shively** (58), biologist, Lincoln, Nebr., July 25; **C. C. Simmons** (76), surgeon and cancer specialist, Boston, Mass., Aug. 15; **Lazarus White** (79), consulting engineer, Larchmont, N. Y., July 30; **William H. Woglom** (74), cancer specialist, New York, N. Y., Aug. 8; **Ivan F. Zarohsky** (61), mechanical engineer, Toledo, Ohio, Aug. 13; **Nicolai Zelinsky** (93), chemist, Moscow, Russia, Aug. 1.

Technical Papers

The X-Ray Dose-Body Size Relationship in Radiation Sickness

W. M. Court Brown[1] and R. F. Mahler[1]

Department of Medicine,
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Since 1949, under the auspices of the Medical Research Council, an investigation has been undertaken into the general effects upon patients of a single therapeutic dose of x-rays. An essential part of this investigation has been the study of the pattern of the symptoms which may be produced by doses of x-rays within the range of integral dose (total energy absorption) of 2½ to 5 megagram-roentgens. A preliminary report (*1*) has shown that the symptom pattern contains three essential phases: the latent period, the period of acute symptoms, and the recovery period, of which the first two only are of importance as far as this communication is concerned. The latent period is defined as the time elapsing from the commencement of irradiation to the onset of symptoms. The onset of symptoms is quite sudden, the two outstanding initial symptoms being nausea and fatigue. By paying repeated visits to the patient, ostensibly for other purposes (e.g., the collection of specimens of blood and urine), it is possible to determine the time of onset of symptoms with considerable accuracy, without influencing the patient by suggestion. To eliminate the possibility that the symptoms were in part psychologically induced by such procedures as being positioned under the x-ray tube, many of the patients were also exposed to sham irradiations; from our experience of the effects of such sham irradiations, we are confident that the symptoms which develop at the end of the latent period are the result of the actual x-irradiation. The period of acute symptoms extends from the time of onset of symptoms to the time when there is clear evidence of an improvement in the condition of the patient, as indicated either by the cessation of vomiting, or by the disappearance of nausea and fatigue when vomiting is absent. Though there is certainly some error in the estimate of the length of this period, our findings indicate that there is a close relationship between the lengths of the two periods, the length of the latent period being inversely proportional to that of the period of acute symptoms.

Previous studies had led us to believe that the length of the latent period was influenced by the integral dose given, tending to be short with high doses and long with low doses. In spite of this belief, a significant correlation was not found between the length of the latent period and the integral dose (*1*); it is now clear that the reason for this was the variation in body size of our patients. The object of this present communication is to report that, if the size of the patient is taken into consideration along with the integral dose, a satisfactory correlation can be obtained with the length of the latent period. As far as the authors are aware, this is the first time in human studies where the size of the individual has been demonstrated to be of importance in considering any biological effect produced by a given dose of x-rays.

Twenty patients, all early cases of ankylosing spondylitis, have been subjected to a single dose of x-rays (Table 1). In each instance the whole of the vertebral column has been irradiated from a point in the midplane 5 cm below the level of the posterior superior iliac spines up to the region of the occipital protuberance. In all 20 patients a field 15 cm × 10 cm in area was used to irradiate the sacroiliac joints, the longer side lying transversely in relation to the line of the vertebral column. In 12 patients the remainder of the length of the column was irradiated by fields 10 cm in width, and in the remaining 8 patients by fields 7 cm in width. Irradiation was given by x-ray tubes energized at 240 kv, the tube current being 18 ma, and the half-value layer of the emergent beam being 1.85 mm Cu. The integral doses were calculated from data obtained by Bong (*2*) and represent the total energy absorbed in the body resulting from both direct and scattered radiations.

TABLE 1

Case No.	Latent period (hr)	Integral dose (megag r)	Weight (kg)	Surface area (m^2)
1	1.5	4.48	46.7	1.35
2	1.75	4.48	62.28	1.73
3	2.00	3.46	51.50	1.57
4	2.50	4.31	63.0	1.80
5	2.50	4.825	57.3	1.68
6	2.75	2.94	50.1	1.50
7	2.75	2.88	62.0	1.72
8	2.75	4.14	54.64	1.62
9	2.75	4.705	73.5	1.85
10	3.00	4.69	63.5	1.75
11	3.00	3.96	61.8	1.76
12	3.00	5.00	70.5	1.83
13	3.00	4.25	48.96	1.46
14	3.50	3.44	68.4	1.85
15	3.75	4.30	57.06	1.70
16	3.75	5.18	63.6	1.98
17	4.25	3.26	68.07	1.89
18	4.33	4.74	87.33	1.98
19	4.50	2.87	55.91	1.59
20	4.50	3.26	64.9	1.74

Twenty pairs of variates are considered, and for any correlation between these to be statistically significant ($P < 0.05$), the value of the correlation coefficient must be greater than 0.4438 (*3*).

When the integral dose alone is compared with the length of the latent period, the value of the correlation

[1] Working for the Medical Research Council. The authors are grateful to Dr. Russell Fraser, Dr. J. F. Loutit, and Dr. L. H. Gray for helpful comments and suggestions.

coefficient is −0.244, and no significance can be attached to this figure. But when the ratio of the integral dose to the body weight is compared with the length of the latent period the value of the correlation coefficient is −0.567, and the correlation is statistically significant. The P value for this correlation is in fact less than 0.01 but greater than 0.001.

When the ratio of the integral dose to the total body surface area is compared with the length of the latent period, the value of the correlation coefficient is −0.529, a value not significantly different from the coefficient obtained when body weight was used.

These findings indicate that if the length of the latent period can be regarded as an indication of one aspect of the biological response to x-radiation, then its length is not only a function of the dose of radiation but also of the size of the individual irradiated. In the opinion of the authors, the dependence of dose upon body size may well indicate that a diffusible metabolite plays an essential role in the development of those symptoms that occur within a few hours of exposure to x-rays.

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A Method for the Quantitative Study of Surface Wounds

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One of the difficulties in the study of wound healing and of factors influencing this process is the lack of quantitative criteria. In the case of cut wounds, measurement of the tensile strength of the scar has been used (*1*). Histological study of granulation tissue has provided some yardstick of the healing process in other types of wounds.

In the case of surface wounds such as burns or pressure sores where one wishes to study the rate of granulation and epithelialization the surface area of the wound constitutes a good objective index of wound healing (*2*).

The following method has been found to give reproducible results in the study of decubital ulcers in man. A Coreco camera is used to take 35-mm Kodachrome photographs of wounds at frequent intervals. This camera provides constant illumination, focal distance, and aperture. The frames of it are modified by superimposing upon them a centimeter scale made of cellophane and placed in such a way that it will show on the photograph in close apposition with the pictured wound. These Kodachromes are projected in a standard enlarger adjusting the magnification so that 1 cm on the screen corresponds exactly to 1 cm on the centimeter scale on the photograph. A thin white cardboard is used as a screen. The outline of the projected wound is drawn upon the cardboard. The tracing is cut out and weighed by means of an analytical balance. Ten squares, measuring 1 cm square, are drawn upon the same piece of cardboard and cut out. These are weighed, the weights are averaged and the figure obtained is used to divide the weights of the various

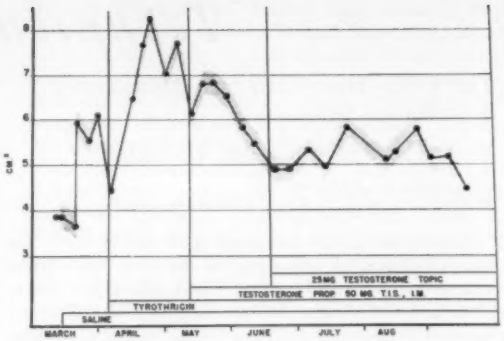

FIG. 1. Long-term study of a patient with hemiplegia showing the quantitative change of the surface of a sacral bed sore under various regimens of treatment. This patient's general condition remained the same throughout. This chart demonstrates the enlargement of bed sores that occurs whenever the treatment is changed; also a distinct deleterious effect of Tyrothricin. The magnitude of the technical error is indicated by the shaded area.

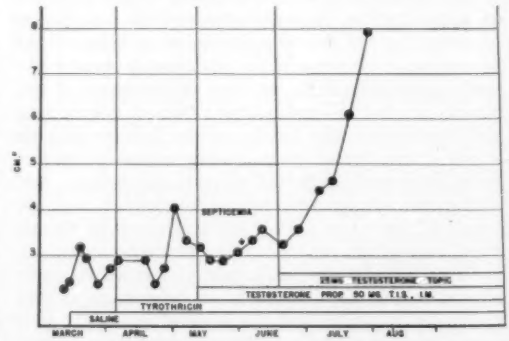

FIG. 2. Shows the same observations as in Fig. 1 although less pronounced, and also the relationship between the size of the bed sore and the general physical state of the patient. This patient developed a septicemia and died, with concurrent enlargement of the bed sore.

[1] The cooperation of George Branche, Jr., Ulfar Jonsson, and Mary Cernius is gratefully acknowledged.

[2] This investigation was performed under a subcontract between the Trustees of Tufts College and The Johns Hopkins University. The basic contract is NONR-248(18) between The Johns Hopkins University and the Office of Naval Research. Opinions and conclusions are those of the author and are not to be construed as necessarily reflecting the view or endorsement of the Navy Department.

wounds projected upon the same cardboard in order to obtain their surface in square centimeters.

This simple method provides a means by objective measurements to make evident changes in the surface of wounds that are not apparent to the naked eye. Figure 1 shows the observations recorded with this method in a man of 42 years of age with hemiplegia and a decubital ulcer over the right buttock. The clinicians who had observed this wound daily had not noticed any remarkable change; however, it is quite obvious that the wound grew larger each time the treatment was changed, and that the use of an antibiotic was followed by a particularly striking enlargement of the lesion. In this instance the procedure of projection and gravimetric planimetry was repeated by different operators and a variation of ±5% was found (indicated by a cross-hatched area on Fig. 1).

Figure 2 shows the same type of observation in a woman with hemiplegia and a decubital ulcer. This patient died from septicemia, and the decubital ulcer worsened with the general condition of the patient.

A method of gravimetric planimetry by standard photographs offers a means to study the course of surface wounds more accurately than by clinical observation or by the pictorial record alone.

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Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, During Sleep[1]

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Slow, rolling or pendular eye movements such as have been observed in sleeping children or adults by Pietrusky (*1*), De Toni (*2*), Fuchs and Wu (*3*), and Andreev (*4*), and in sleep and anesthesia by Burford (*5*) have also been noted by us. However, this report deals with a different type of eye movement—rapid, jerky, and binocularly symmetrical—which was briefly described elsewhere (*6*).

The eye movements were recorded quantitatively as electrooculograms by employing one pair of leads on the superior and inferior orbital ridges of one eye to detect changes of the corneo–retinal potential in a vertical plane, and another pair of leads on the internal and external canthi of the same eye to pick up mainly the horizontal component of eye movement. The potentials were led into a Grass Electroencephalograph with the EOG[3] channels set at the longest time constant. Brain waves, lid and jaw muscle activity, and electrode movement introduced superfluous potentials which severely hindered the identification of eye movement potentials. To eliminate this difficulty, a monopolar recording was made simultaneously from the frontal area (and occasionally from the anterior temporal area) to be compared with the bipolarly recorded electrooculogram. In this way, the eye movement potential could be recognized easily as a wave in phase on the monopolar and bipolar recordings, but with a potential from 2 to 4 times greater on the latter recording. Note that the gain settings (Fig. 1) for the bipolar recording (RV) and monopolar recording (RF) were adjusted so that an equal excursion of both pens signified that the bipolar potential was actually 4 times greater than the monopolar potential. The criterion for identification of eye movement was confirmed by direct observation of several subjects under both weak and gradually intensified illumination. Under the latter condition, motion pictures were taken of 2 subjects without awakening them, thereby further confirming the validity of our recording method and also the synchronicity of eye movements.

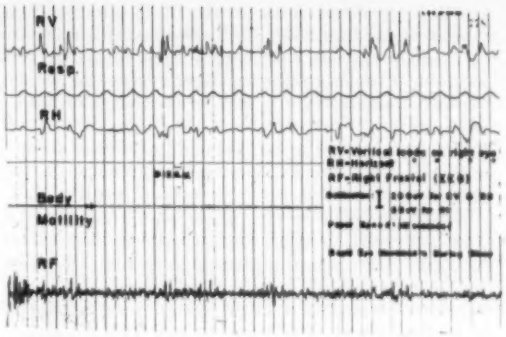

Fig. 1. Sample record exhibiting rapid eye movements in a sleeping subject. RV = vertical leads on right eye; RH = horizontal leads on right eye; RF = right frontal (EEG). Calibration: { 200 μv for RV & RH / 50 μv for RF } ; paper speed: 10 sec.

Twenty normal adult subjects were employed in several series of experiments although not all the subjects were involved in each series. To confirm the conjecture that this particular eye activity was associated with dreaming, 10 sleeping individuals in 14 experiments were awakened and interrogated during the occurrence of this eye motility and also after a period of at least 30 min to 3 hr of ocular quiescence. The period of ocular inactivity was selected on the basis of the EEG pattern to represent, as closely as possible, a depth of sleep comparable to that present during ocular motility. Of 27 interrogations during ocular motility, 20 revealed detailed dreams usually involving visual imagery; the replies to the remaining 7 queries included complete failure of recall, or else, "the feeling of having dreamed," but with inability to

[1] Aided by a grant from the Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

[2] Public Health Service Research Fellow of the National Institute of Mental Health.

[3] Electrooculogram.

recollect any detail of the dream. Of 23 interrogations during ocular inactivity, 19 disclosed complete failure of recall, while the remaining 4 were evenly divided into the other 2 categories. Recognizing the inadequacies of employing a χ^2 test for the independence of the 2 groups of interrogations, the probability nevertheless on a χ^2 basis is that the ability to recall dreams is significantly associated with the presence of the eye movements noted, with a p value of less than 0.01.

Eleven subjects in one series of 16 experiments were permitted to sleep uninterruptedly throughout the night. The mean duration of sleep was 7 hr. The first appearance of a pattern of rapid, jerky eye movements was from 1 hr 40 min to 4 hr 50 min (3 hr 14 min, mean) after going to bed. This pattern of eye motility was of variable duration and frequently disappeared for a fraction of a minute or for several minutes only to reappear and disappear a number of times. The period from the onset of the first recognizable pattern to the disappearance of the last pattern was from 6 to 53 min with a mean of 20 min. A second period of eye movement patterns appeared from 1 hr 10 min to 3 hr 50 min (2 hr 16 min, mean) after the onset of the first eye motility period. With lengthier sleep there occurred a third and, rarely, a fourth such period. The electrooculogram disclosed vivid potentials with amplitudes as high as 300–400 μv, each potential lasting about 1 sec. This was further striking in comparison with simultaneously recorded monopolar EEG's, from the frontal and occipital areas, which were invariably of low amplitude (5–30 μv) and irregular frequency (15–20/sec and 5–8/sec predominating).

In another series of experiments involving 14 subjects, the respiratory rate was calculated for a minimum of ½ min during eye motility and compared with the rate for a similar duration 15 min before and after an eye motility period. The respiratory rate had a mean of 16.9/min during eye motility in contrast with 13.4/min during ocular quiescence. By using Fisher's t method, the difference in rates was found to be statistically significant with a probability of less than 0.001. Experiments now in progress suggest that heart rate also is probably higher in the presence of these eye movements. Body motility records were secured in 6 experiments by attaching a sensitive crystal to the bed spring and leading the output through a resistance to a Grass preamplifier. In every case the eye motility periods were associated with peaks of overt bodily activity although the latter were frequently present in the absence of eye movments.

Data obtained from the 2 female subjects used in these experiments were at least qualitatively similar to that obtained from males.

The fact that these eye movements, EEG pattern, and autonomic nervous system activity are significantly related and do not occur randomly suggests that these physiological phenomena, and probably dreaming, are very likely all manifestations of a particular level of cortical activity which is encountered normally during sleep. An eye movement period first appears about 3 hr after going to sleep, recurs 2 hr later, and then emerges at somewhat closer intervals a third or fourth time shortly prior to awakening. This method furnishes the means of determining the incidence and duration of periods of dreaming.

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Inactivating Medium for Hexachlorophene (G-11) Types of Compounds and Some Substituted Phenolic Disinfectants

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A previous report presented evidence of the use of synthetic, nonionic wetting agents for the inactivation of the bacteriostatic activity of hexachlorophene (G-11) upon bacteria (*1*). With the evidence obtained of the marked interfering action of Tween-80[2] on the bacteriostatic effects of hexachlorophene, it appeared desirable to extend these studies to several other chemical disinfectants, two of which are closely related in chemical constitution to hexachlorophene, G-4 (2,2′-dihydroxy-5,5′-dichlorodiphenylmethane) and Actamer (2,2′-dihydroxy-3,5,3′,5′-tetrachlorodiphenyl sulfide). In addition to the latter, several substituted phenolics and related compounds were evaluated in the presence and absence of the nonionic surface-active agent. The compounds studied and their chemical designations are given in Table 1.

Due to the relative insolubilities of several of the compounds in distilled water (Nos. 1–8) these were first dissolved in 1 ml of 10% sodium hydroxide and then diluted to 1.0% with distilled water. The remaining disinfectants were dissolved directly in distilled water or in beef extract broth (0.3% Bacto beef extract, 1% Bacto peptone, 0.5% sodium chloride in water). In all instances 9 ml of sterile broth, with or without 1% Tween-80, were added aseptically to the first of a series of sterile test tubes and 5-ml amounts in the remaining, or 9 additional tubes. To the first tube was added 1 ml of the stock germicide to be tested. After thoroughly mixing the latter in the medium, 5 ml was transferred to the second tube containing 5 ml of broth. This process of mixing and transferring was then continued through the remain-

[1] Present address, Los Angeles County Health Department, Calif.

[2] Atlas Powder Company, Delaware, brand of polyoxyalkylene derivative of sorbitan monooleate.

TABLE 1

TRADE NAMES AND CHEMICAL CONSTITUTION OF DISINFECTANTS

Trade name	Chemical constitution	Manufacturer
1. G-11	2,2′-Dihydroxy-3,5,6,3′,5′,6′-hexachlorodiphenylmethane	Sindar Corporation, New York.
2. G-4	2,2′-Dihydroxy-5,5′-dichlorodiphenylmethane	Sindar Corporation, New York.
3. Actamer	2,2′-Dihydroxy-3,5,3′,5′-tetrachlorodiphenylmethane	Monsanto Chemical Co., St. Louis, Mo.
4. Santophen-1	Orthobenzyl-para-chlorophenol	Monsanto Chemical Co., St. Louis, Mo.
5. Dowicide-4	2-Chloro-4-phenylphenol (85%)	Dow Chemical Co., Midland, Mich.
6. Dowicide-A	Sodium orthophenylphenate	Dow Chemical Co., Midland, Mich.
7. Dowicide-2	2,4,5-Trichlorophenol	Dow Chemical Co., Midland, Mich.
8. Dowicide-32	Mixture of 4-chloro-2-phenylphenol and 6-chloro-2-phenylphenol	Dow Chemical Co., Midland, Mich.
9. Lysol	Orthohydroxydiphenyl with soap, alcohol, cresylic acid, propylene glycol, glycerol, and water	Lehn and Fink, Corp., Bloomfield, N.J.
10. Osyl	Potassium ricinoleate, orthohydroxydiphenyl, alcohol, propylene glycol, glycerol, and water	Lehn and Fink, Corp., Bloomfield, N.J.
11. Amphyl	Potassium ricinoleate, orthophenylphenol, para-tertiary-amyl phenol, alcohol, propylene glycol, glycerol, and water	Lehn and Fink, Corp., Bloomfield, N.J.
12. Phenol	Hydroxybenzene—	—
13. Metaphen	4-Nitroanhydrohydroxymercury orthocresol	Abbott Laboratories, North Chicago, Ill.
14. Mercresin	Orthohydroxyphenylmercuric chloride, secondary amyltricresols, alcohol, and acetone	Upjohn Company, Kalamazoo, Mich.
15. Hexylresorcinol	Hexylresorcinol (0.1%) in a glycerol-water solution.	Sharp and Dohme, Co.

ing tubes; finally, 5 ml of the test solution was discarded from the last tube.

The germicide-broth dilutions were inoculated with a 4-mm loopful of a 24-hr-broth culture of *Micrococcus pyogenes* var. *aureus* and incubated for a week, during which time the presence or absence of visible growth was recorded. In those instances where a turbid solution resulted upon adding the germicides to broth or a similar condition resulted upon combining the germicides with the Tween-80 broth, these mixtures were tested for the presence of viable bacteria at the end of 48-hr incubation by transferring a 4-mm loopful of the suspension to tubes containing sterile broth and broth with 1% Tween-80. The latter tubes were also incubated at 37° C for several days. The results of this study are presented in Table 2.

From the data given in the table it may be noted that with the exceptions of Mercresin and phenol, the remaining germicides are markedly affected by Tween-80 in so far as their bacteriostatic activities are concerned. The exceptionally high bacteriostatic actions of the hexachlorophene types of compounds (G-11, G-4, Actamer) is evident from these results in which approximately 1 part of these compounds in 2,000,-000–5,000,000 parts of plain broth inhibited the growth of *M. pyogenes*, var. *aureus*. However, when the same test was carried out in the presence of Tween-80 in broth, concentrations greater than 1:1000 of the G compounds and a 1:2000 concentration of Actamer are required to inhibit the growth of the same organism. A distinct interfering action was also obtained with the nonionic agent against Santophen-1 and Dowicide-A. The remaining Dowicides, Metaphen, hexylresorcinol, and the cresylic acid types of disinfectants showed somewhat less, but a fairly proportionate loss in activity when tested in the presence of Tween-80.

Preliminary studies reveal that Tween-80 will interfere with the antibacterial activity of certain quaternary ammonium surface-active germicides and the antibiotic tyrothricin. No inhibition was noted in the use of the nonionic agent against the activities of penicillin, streptomycin, aureomycin, neomycin, chloromycetin, bacitracin, and terramycin against *M. pyogenes*, var. *aureus*. While this report primarily proposes the use of nonionic surface-active compounds for distinguishing between the bactericidal and bacteriostatic activities of certain antimicrobial agents,

TABLE 2

INHIBITING EFFECTS OF TWEEN-80 ON SOME SUBSTITUTED PHENOLICS

Disinfectant	Limiting dilution inhibiting in plain broth	Limiting dilution inhibiting in 1% Tween-80 in broth
1. G-11	1 : 2,048,000	< 1 : 1,000*
2. G-4	1 : 5,096,000	< 1 : 1,000
3. Actamer	1 : 2,048,000	1 : 2,000
4. Santophen-1	1 : 128,000	< 1 : 1,000
5. Dowicide-4	1 : 32,000	1 : 2,000
6. Dowicide-A	1 : 4,000	< 1 : 1,000
7. Dowicide-2	1 : 64,000	1 : 4,000
8. Dowicide-32	1 : 64,000	1 : 2,000
9. Lysol	1 : 3,200	1 : 200
10. Osyl	1 : 2,560	1 : 160
11. Amphyl	1 : 5,120	1 : 320
12. Phenol	1 : 400	1 : 200
13. Metaphen (1 : 500 aq.)	1 : 2,560	1 : 640
14. Mercresin (1 : 250 tinc.)	1 : 5,120	1 : 2,560
15. Hexylresorcinol (1 : 1,000)	1 : 20	< 1 : 5

* Figures preceded by symbol < indicate highest concentration of disinfectant tested failed to inhibit growth of organisms.

it also poses the question concerning the indiscriminate use of the nonionics as solubilizing, wetting, or detergent agents in various germicide and drug formulations without preliminary biological compatibility data.

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A Rapid Titrimetric Method for Determining the Water Content of Human Blood[1]

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The use of the Karl Fischer reagent to determine blood and tissue water *in vivo* and *in vitro* in rats has been reported by Cook, Cramer, and Kenyon (*1*). Such a method, if applied to human beings, may have physiological, diagnostic, and therapeutic applications, since a determination can be made in a matter of 10 min. The most convenient tissue to use is the blood, which is relatively sensitive to changes in body water.

References to the literature have given rather diverse and incomplete figures for human plasma water and whole blood water. The accompanying chart shows this diversity.

TABLE 1

Reference	Total H_2O whole blood %	Plasma water %	Cellular water %
U.S.A.F. (*2*)	83(81–86)	94(93–95)	72(70–75)
Cushny (*3*)		90–93	
Best & Taylor (*4*) (Modified after Cushny)		92	
Everett (*5*)		92	65
Davis, Kenyon, Kirk	80.5(79–82)	92.4(91–93)	66(63–70)

To obtain values of blood water in normal humans by the Karl Fischer method, we obtained an unselected group of blood donors at the Los Angeles County Hospital. Our procedure is as follows. A small amount of venous blood is drawn into a medicine dropper. Capillary blood from a finger puncture can also be used (*1*). The medicine dropper is weighed and one drop of blood (more would obscure the end point) is discharged into a flask containing 20 ml of anhydrous methanol previously brought to an orange-red end point with Fischer reagent. The medicine dropper is again weighed and the flask is brought to the same orange-red end point by titrating a measured volume of Fischer reagent. The Fischer reagent is dispensed from an anhydrously maintained all-glass buret assembly.

[1] Support for this study from Harold V. Kirk and Edward Pollard is gratefully acknowledged.

TABLE 2

Substance	Percentage water found by: Oven drying	Percentage water found by: Titration (Av. of duplicate samples)
Whole blood	80.2	80.2
	80.5	80.0
	80.2	79.9
Plasma	92.3	91.5
	92.6	91.6
	92.0	91.6
	90.8	90.4
	91.3	90.5

By using a special double necked flask containing a twin platinum electrode and attached to an aquameter, an electrometric end point can also be used. Up to 8 drops of blood can be used in this instance, hence greater accuracy can be obtained. However, we found that both methods gave the same values on the same blood. All of the work reported in this paper was done using the electrometric end point method.

Mitchell and Smith (*6*) have written the only book on the subject at the present time, but we found the methods and formulae for the Fischer reagent used by Shell Development Company, Emeryville, California, to be superior in producing a more stable end point. We strongly advise against using the commercially available material as the end point is extremely unstable.

Hematocrit values by the Wintrobe method and specific gravity values by the copper sulfate method were routinely done on the same samples.

In all, 100 whole blood samples were used including 23 females and 77 males. The female extremes were 78 and 84%. The average was 80.8% and the bulk of the samples fell in the range 80–82%. The male extremes were 74 and 84%. The average was 80.4% and the bulk of the samples fell in the range 79–82%. The combined average was 80.5%.

We found a nonsignificant correlation of -0.17 between the percentage whole blood water and the hematocrit. We found a significant correlation of -0.49 between the specific gravity and the percentage whole blood water. There was no correlation between age and percentage whole blood water.

A smaller group of 15 additional samples was obtained in the same manner. The whole blood water was obtained and the samples were then centrifuged. The plasma water content was obtained and the cellular water content calculated. Extremes of whole blood were 76–84% with an average of 80.5%, the bulk falling between 79 and 83%. Plasma water extremes were 90 and 94%. The average was 92.5%, the bulk falling between 91 and 93%. The cellular water extremes were 56 and 74%, the average was 66% and

the bulk fell between 63 and 70%. A no more significant correlation than −0.47 (due to the smaller sample size) between the percentage whole blood water and the hematocrit was obtained.

Duplicate samples of plasma were run by the oven method and the Karl Fischer method. On the whole, the two methods check within about 1%, but the oven method tended to yield higher percentages. This fact further substantiates the validity of the method. The results are as shown in Table 2, expressed as percentage of water.

The titrimetric estimation of water content of a large array of whole blood and plasma samples may be obtained with great rapidity using the Karl Fischer reagent; 10 min is the upper limit of time consumed.

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Perception by the Skin of Electrically Induced Vibrations

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If the dry skin of one's finger is moved gently over a smooth metal surface covered with a thin insulating layer, and the metal is connected to the ungrounded side of a 110-v power line, the surface has a characteristic feeling that disappears when the alternating voltage is disconnected. It is the purpose of this note to describe some observations concerning this effect and to suggest an explanation which may be of some interest, particularly to those who have experienced the effect without realizing its cause.

In the summer of 1950, E. Mallinckrodt noted that a certain shiny brass electric light socket did not feel as smooth when the light was burning as it did with the light off. It was soon discovered that when the light was turned on with the socket key, the socket was connected to the live wire (presumably because of imperfect insulation). If one reversed the plug in the floor receptacle the sensation ceased because the socket was then connected with the ground instead of the live side of the line, and there was no possibility of current flowing through one's body. The sensation was slight but definite when current (which later proved exceedingly minute) was flowing, and can best be described as a lack of smoothness or a feeling of vibration as one passes his fingers gently over the surface, such as might be caused by a small amount of resin. The sensation was considerably diminished if one changed from leather to rubber-soled shoes, and increased if one moved his stockinged foot from the high-resistance wooden floor to the brick of the fireplace which extended into the ground.

The effect was then noted in varying degrees (and confirmed by other observers) in a wide variety of objects when connected to the live wire and stroked with the fingers: for example, a lightly varnished brass door knob, an ordinary lacquered beer can, an egg in an electric egg boiler as the steam dried off. The hands of some individuals are more sensitive than others, and different parts of the hand yield different responses. Breathing upon the skin diminishes its sensitivity temporarily.

In an experiment made to investigate the effect quantitatively, an aluminum plate was connected to the ungrounded side of the 60-cycle, 110-v power supply through a variable current-limiting resistance. Half of the plate was coated with a very thin layer of an insulating varnish (Krylon). A man, standing on a Lucite insulator, touched the aluminum plate with one hand while the other was grounded through a meter by which the current passing through him could be measured. On drawing his finger lightly across the thinly varnished part of the plate, the peculiar resin-like sensation was felt. No such effect was observed when the finger was drawn in the same manner across the unvarnished part of the metal plate. With the highest current-limiting resistance used (22 megohms) the current through the man was about 1 μamp when the finger was drawn across the varnished part and the sensation was felt. It was 4 μamp on the unvarnished part, and no sensation was felt. The effect was also perceived on an insulated surface when the observer's body was completely insulated from ground, and all the alternating current that flowed (less than 10^{-7} amp) did so by way of body to ground capacitance. The effect diminished as the observer moved farther from the floor on a ladder. No effect whatever was obtained with direct current.

These data suggested that the effect was not due to direct action of current on the sense organs. If, instead of the finger, the thinner skin of the nose is touched to the uninsulated part of the plate and the series resistance made small enough, an intermittent sharp pricking can be felt. This is direct stimulation of sensory nerve endings by current and is an entirely different sensation from the resiny feeling observed when electric charges are not passing through the skin. The resiny effect can also be felt on the uninsulated surface if skin is used that is thin and very dry. In this case, the keratin outer layer of skin has a high resistance and acts as the insulating layer. If the edge of the ear is used under favorable conditions, a 120-cycle tone can be heard.

In order to show that touch or pressure receptors are sensitive enough to detect mechanical vibrations due to the attraction of charges under similar conditions, a condenser was made from two pieces of aluminum foil with slightly wrinkled tissue paper between. When the power line was connected across this condenser and the hand was placed gently on the aluminum sheet in contact with the grounded side, vibrations could be felt in places where the spacing happened to be favorable. Here, in contrast to the preceding experiments, the man was not in the circuit, so no current flowed through him, and the vibration could be felt whether or not the hand stroked the surface.

These observations lead us to this explanation of the original effect. The insulating layer, or the very dry outer skin, forms the dielectric of a condenser, of which the metal is one plate and the conducting fluids of the body the other. When an alternating voltage is applied to this condenser, there is an intermittent attractive force between the skin and the metal. If the hand remains stationary, the skin is not springy enough to allow perceptible motion around the receptors and there is no sensation. However, when the hand is moved with light pressure, friction between the skin and plate is increased as the condenser is charged, so there is an intermittent drag and release which does activate receptors and the surface feels resiny. The effect is not present when the finger is wet, because then the skin has a low resistance; the forces developed across the varnish are between the water outside the skin and the metal, and friction between finger and surface is not appreciably affected by the varying charge on this metal-water condenser. In general most of the energy for stimulating comes from the motion of the hand, and where the sensation is present this is modulated by the alternating electrical forces. Since these forces decrease as current decreases, the perceptibility of the effect when the body is completely isolated from ground is a striking demonstration of the high sensitivity of cutaneous receptors.

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The Resolution and Fungistatic Action of 1,4-Cyclohexanediol bis(bromoacetate)

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In examining organic substances so as to correlate fungicidal activity with chemical structure, it is intriguing, as in other studies of physiological activity, to note the variation in activity often caused by slight changes in molecular structure, especially optical or geometric isomers. The purpose of this report is to record some of the work done with the geometric isomers of 1,4-cyclohexanediol bis(bromoacetate).

TABLE 1

FUNGUS INHIBITION OF GROWTH OF A FUNGUS BY ISOMERS OF 1,4-CYCLOHEXANEDIOL BIS(BROMOACETATE)

Molar concentration	% retardation of growth		
	cis-trans	*cis*	*trans*
10^{-2}	100	100	60
10^{-3}	40	100	34
10^{-4}	12	31	15
10^{-5}	6	8	3

1,4-Cyclohexanediol was prepared by the method of Adkins and Cramer (*1*). This product was esterified by dissolving one-half mole (58 g) in 2000 ml of benzene and adding dropwise one mole (202 g) of bromoacetyl bromide. After the addition was completed, the mixture was maintained at gentle reflux for 5 hr (or until evolution of hydrogen bromide ceased) whereupon the benzene was removed by distillation. A brown residue weighing 152 g (84% yield) remained. This material was considered to contain equivalent quantities or nearly so, of both isomers since Olberg *et al.* (*2*) have shown that a similar preparative procedure for 1,4-cyclohexanediol yielded nearly equivalent quantities of both *cis* and *trans* forms.

The crude bromoacetate was recrystallized from hot 95% ethanol and the crystals obtained were washed with ether to remove the *cis* ester selectively, leaving on the filter the more insoluble *trans* isomer. The *trans* isomer was then repeatedly recrystallized from ethanol until a constant melting point of 137° was obtained. Ten grams of *trans* ester were refluxed with 19 g of barium hydroxide in water. The solution was evaporated to dryness, extracted with hot acetone, and this solution was concentrated and cooled. One gram of white crystals (30% yield) was obtained melting at 143.5–145°. This agrees substantially with Olberg's value (*2*) of 142° for the *trans* 1,4-diol confirming the assignment of *trans* to the bis(bromoacetate) melting at 137°.

The ether solution of impure *cis* isomer (contaminated with *trans* in the separation) was evaporated to dryness; and the brown crystalline residue was dissolved in acetone, decolorized with Nuchar, and cooled in a dry ice–isopropanol bath. The crystalline *cis* 1,4-cyclohexanediol bis(bromoacetate), remaining, melted at 114–115°. Recrystallization from acetone or benzene-ligroin solvent mixture failed to elevate the melting point above this value. In order to have sufficient compound for fungicidal assay, hydrolysis to the *cis* 1,4-diol was not carried out.

The fungistatic activity of the mixture and pure isomers was determined using the method previously used by this laboratory (*3*), in which the indices of toxicity are the radial growth rates of the test organism at the various concentration levels of toxic material.

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Table 1 gives these data against *Trichoderma viride* USDA T-1.

These data show the *cis* compound to be considerably more fungistatic than the corresponding *trans* compound. No conclusive reason for this behavior is now available.

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Preliminary Observation on a Hatching Stimulus for *Aedes* Eggs (*Culicidae*)

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Many aedine mosquitoes have a diapause in the egg stage. This diapause may be an obligate one or one brought on solely by adverse conditions. Diapause may be broken in various ways but often an additional stimulus is necessary for hatching. In experimental work it is important that hatching of the eggs occurs whenever desired. Moreover, ecological studies on such problems as succession of species require a knowledge of the factors which influence hatching. For example, why do the eggs of *Aedes campestris* Dyar and Knab hatch in the field in the region of Churchill, Manitoba, so much later than do those of *Aedes hexodontus* Dyar? These considerations make an understanding of hatching stimuli of interest.

Recent experiences with the hatching of *A. campestris* eggs and with *A. hexodontus* eggs have led to the conclusion that there may be some factor in an infusion of decaying mosquito bodies that stimulates hatching of these eggs at an appropriate temperature. Table 1 describes the experiments carried out and the results obtained.

Gjuillin *et al.* (*1*) found low dissolved oxygen of the hatching medium to be a factor stimulating *A. vexans* (Meig.) eggs to hatch. Therefore, it was decided to try a medium of low dissolved oxygen content with *A. campestris* eggs. In our experiments there was no hatch in distilled water at normal pressure, in distilled water subjected to reduced pressure to remove oxygen, or in distilled water over pyrogallol. Abdel-Malek (*2*) and Horsfall (*3*) found plant hormones to be a factor in the hatching of *Aedes* eggs; but for us a solution of 1 : 10 or 1 : 100 of indoleacetic acid in water gave no results with *A. campestris*.

It is interesting that Mail (*4*) kept *A. campestris* eggs in pond water for 20 months at a temperature between 0 and 10° C and when he returned them to 22° C he got a 25% hatch. There may have been some substance in the pond water similar to that which is present in the bacteria and mold infusion.

A. hexodontus eggs will hatch just above 0° C,

[1] The author wishes to acknowledge the valuable assistance rendered by T. P. Copps, C. A. Barlow, and D. A. Smith of the Defence Research Northern Laboratory.

TABLE 1

Hatching Results with Eggs of *Aedes campestris* and *Aedes hexodontus* in an Infusion of Decaying Mosquitoes

Expt. No.	Species	Number of eggs and history	Treatment	Results	Comments
1	*A. hexodontus* *A. excrucians* *A. campestris*	Unknown number stored together on filter paper with decaying mosquitoes. 15 days old.	Distilled water added.	First instar larvae of *A. campestris* appeared on 3rd day. No eggs of other species hatched.	No attempt was made to determine % of *A. campestris* that hatched since the eggs of the 3 species overlap in size.
2	*A. campestris*	150 eggs 15 days old, stored on clean filter paper.	Placed in infusion of decaying adult mosquitoes.	30% of the viable eggs hatched over a 3-day period.	A control of 150 eggs in distilled water gave a hatch of one larva. On dissection, the embryos were viable.
3	*A. campestris*	50 eggs stored 4 months in distilled water at between 4 and 10° C.	Placed in infusion of decaying first instar larvae.	90% of the viable eggs hatched within 24 hr at 25° C.	A control of 25 eggs in distilled water gave no hatch in 15 days at 25° C. On dissection, the embryos were viable.
4	*A. hexodontus*	250 eggs exposed to cold for 6 months to break diapause were placed in distilled water at 20° C for 5 days. No hatch resulted.	Half the eggs were then placed in an infusion of decaying mosquitoes.	In the infusion over 50% of the eggs hatched.	The exact % was not recorded. In the control there was no hatch. On dissection the embryos were viable.

whereas *A. campestris* eggs will do so only at considerably higher temperatures. It was originally thought that temperature alone was responsible for the delay in hatch of *A. campestris* in the field. However, it may be that temperature is only a limiting factor in the action of a hatching stimulus from decaying organic matter.

It is possible that an infusion of bacteria and molds growing on decaying mosquito bodies will stimulate eggs of other species of *Aedes* to hatch. Many references in the literature suggest that microorganisms often play a part in the hatching of *Aedes* eggs (*5*). Bacteria and molds are now being isolated from decomposing mosquitoes, and further experiments on the effect of these microorganisms and extracts from them are in progress.

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New Chelating Agents for Trivalent Iron

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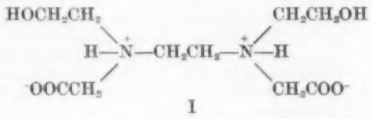
There have been developed in these laboratories two metal ion chelating agents that show promise as iron carriers for the treatment of iron chlorosis in plants (*1*). These compounds are N,N′-dihydroxyethylethylenediaminediacetic and N-hydroxyethylethylenediaminetriacetic acids.[1] The amino acids, having the structures I and II, are new compounds which have been prepared and



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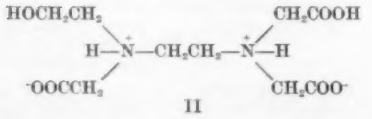

II

purified by methods to be reported subsequently (*2*).

[1] F. C. Bersworth, patents pending.

The acid dissociation constants and the interactions of the various acid species with ferric ions were determined for both I and II by potentiometric measurements of pH in a manner similar to that described for N,N-dihydroxyethylglycine (*3*). The reactions investigated and the corresponding equilibrium constants may be summarized as follows.

N,N′-Dihydroxyethylethylenediaminediacetic Acid (I)

$H_2A(OH)_2 \rightleftarrows HA(OH)_2^- + H^+$	$pK_1 = 4.7$
$HA(OH)_2^- \rightleftarrows A(OH)_2^{-2} + H^+$	$pK_2 = 8.6$
$Fe^{+3} + A(OH)_2^{-2} \rightleftarrows FeA(OH)_2^+$	$\log K_1 \leq 15$
$FeA(OH)_2^+ \rightleftarrows FeAO(OH) + H^+$	$pK_2 = 2.2$
$FeAO(OH) \rightleftarrows FeAO_2^- + H^+$	$pK_3 = 5.5$

N-Hydroxyethylethylenediaminetriacetic Acid (II)

$H_3A(OH) \rightleftarrows H_2A(OH)^- + H^+$	$pK_1 = 2.6$
$H_2A(OH)^- \rightleftarrows HA(OH)^{-2} + H^+$	$pK_2 = 5.1$
$HA(OH)^{-2} \rightleftarrows A(OH)^{-3} + H^+$	$pK_3 = 8.3$
$Fe^{+3} + A(OH)^{-3} \rightleftarrows FeA(OH)$	$\log K_1 \leq 21$
$FeA(OH) \rightleftarrows FeAO^- + H^+$	$pK_2 = 3.8$

The most important property of these chelating agents is their ability to form 1:1 ferric chelates of sufficient strength so that the complexed trivalent iron is stabilized against hydrolysis even in strong alkaline solutions. Thus, while the ferric ethylenediaminetetraacetate complex is decomposed in alkaline medium to ferric hydroxide, the corresponding ferric chelates of these hydroxyethyl derivatives are completely stable against hydroxide precipitation. The resistance of these ferric complexes to hydrolytic decomposition results from the fact that 1:1 chelate formation is accompanied by the simultaneous ionization of the weakly acidic ethanolic protons of the hydroxyethyl groups.

Both amino acids function as hexadentate chelating agents in the presence of ferric ions. The hexacoordinated ferric ion is bound to the ligand through the two nitrogen and four oxygen atoms.

The development of N,N′-dihydroxyethylethylenediaminediacetic and N-hydroxyethylethylenediaminetriacetic acids makes possible the study and treatment of chlorosis conditions in calcareous soils as well as other studies in alkaline medium. Further investigation of the properties of these chelating agents is in progress and will be reported soon.

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Comments and Communications

Improvement in Frost Resistance of Parsnip Tops Sprayed with Chemical Growth Substances

THERE is extensive literature on various responses of plants to synthetic growth substances, but, so far as we know, there have been no reports on apparent improvement in frost resistance of plant foliage sprayed with such chemicals. The present communication deals with evidence of this nature arising out of field experiments with parsnips (*Pastinaca sativa*) at Edmonton.

Test material was grown from seed of the variety Hollow Crown, planted May 22, 1952 in 40-ft rows per plot in quadruplicate randomized blocks and was sprayed with various chemicals on September 6 of the same year. A month later the first frosts occurred with minimum night temperatures of 25° F on Oct. 3, 17° F on Oct. 4, 17° F on Oct. 5, and 25° F on Oct 6. Observations on Oct. 7 showed that in every replicate, tops of plants sprayed with 2,4,5-trichlorophenoxypropionic acid (Dow, Color Set) or with sodium naphthaleneacetate (Dow, App-L-Set) at 1 lb active chemical in 50 gal water per acre, were virtually uninjured by frost. On the other hand, most of the leaves of check material were collapsed and darkened. Tops of treated plants remained erect and green until more severe frost occurred several weeks later (Nov. 26, 5° F).

Prior to the first frost the chemical treatments caused perceptible, but not severe, brittleness in leaf stalks together with retardation of growth of the main fleshy root and an abundant development of fine lateral roots.

Apparently a hardening-off process in the parsnips was intensified by the spray ingredients. Further research to determine range of variability of response and to study its nature during the first and second years' growth of this biennial and of other unrelated crops is underway.

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The First Circuit for an Electrical Logic-Machine[1]

IT IS usually assumed that the performance of logical inference by electrical relay machines is of comparative recent date. However, in Baldwin's *Dictionary of Philosophy and Psychology* (1902) there is a reference to an electrical logic-machine designed by Alan Marquand (1853–1924), fellow in philosophy, Johns Hopkins University, and afterwards professor of archeology and the history of art at Princeton University.

Professor Alonzo Church of Princeton recently looked through the Marquand manuscripts now in the Princeton University Library and discovered a wiring diagram which he thought important for us to see, as it was not mentioned in any of the published papers he could recall. Prepared about 1885, it is probably the first circuit of an electrical logic-machine, and is presumably the one referred to in Baldwin's dictionary article.

Marquand had originally constructed in 1883 a four-term logic-machine operated mechanically (*Proc. Am. Acad. Arts and Sci.*, 1885). The dial plate of Marquand's machine had 16 small pointers rather like watch hands, representing the 16 logical combinations of the four terms *A, B, C, D*, and their negations represented by the small letters, *a, b, c, d*. They were as follows:

Each of the pointers numbered *1–16* is able to indicate the "truth" or "falsity" of the combinations they represent. When at the horizontal, the pointer has the value "truth," when at the vertical the value "falsity." Reading down each column in turn, the left uppermost pointer, *1*, represents the combination *A, B, C, D*, and so on until we reach the right lowermost pointer, *16*, which is *a, b, c, d*. We are thus given a mechanical truth table for four terms.

The diagram which was apparently meant to operate this machine is made up of two circuits both wired in series and parallel. As we now know switches wired in series can represent a logical product and in parallel a logical sum. Marquand probably made this application intuitively since this diagram is merely an electrical translation of his geometrical diagram for *n* terms. (*Philos. Mag.*, Oct., 1881).

Each circuit is operated by a separate battery. The letter key circuit connected to eight one-way switches (i.e., the letter keys, representing the terms and their negatives) is wired to *16* electro-magnets, each of which represents a combination from *1* to *16* (only one armature of the electro-magnets is shown). Each letter key functions negatively, actuating those electromagnets (and hence pointers) which include in their combinations the negation of this letter; the answer is read off in negative form from the fallen pointers. If,

[1] We have to thank Mr. Savage, archivist of Princeton University Library, Professor Church and Mrs. Eleanor Marquand Delanoy.

for example, the letter key A is pressed, the a electro-magnets are actuated, this sustains the a pointers (i.e., the A's drop to the vertical when the operation key is set to position *3*). If the a key is pressed the A pointers are similarly sustained, and so on for other positive and negative letter keys.

The operation key circuit worked by a separate battery is connected to the *16* electro-magnets through a three-way switch, "the operation key" (the 2nd position of which is wired to a rheostat). Position *1* of the operation key raises all the fallen pointers to the horizontal thus indicating the logical universe or truth-table for four terms; it prepares the machine for a new problem. Position *2* sustains the pointers at the horizontal (it passes sufficient current to sustain the armatures of the electro-magnets actuated by the letter key operations) but does not raise the fallen pointers. Position *3*, which switches off operation key circuit, causes unsustained pointers to fall.

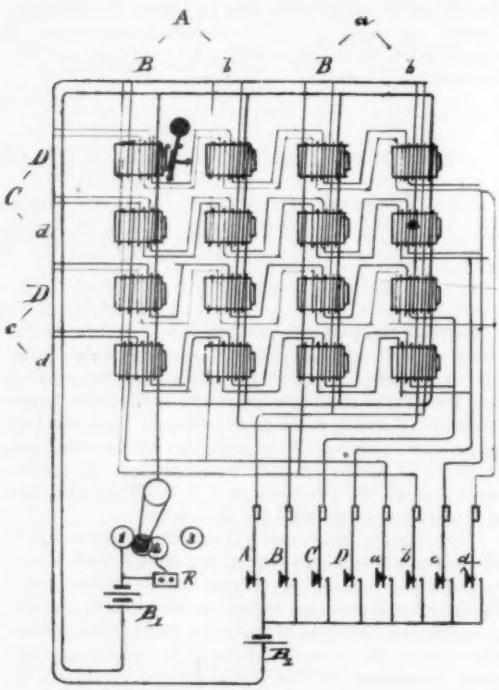

FIG. 1.

On Marquand's system the premises are inserted in a negative form. For example, the premise $A \supset B$ (A implies B) in Marquand's notation $A \prec B$, is identical with $-(A.\ -B)$ (it is false that both A and not B are true) or as he expresses it $A\ b \prec 0$; the premise $B \supset C$ is translated into $-(B.\ -C)$ or $Bc \prec 0$.

In operating the machine, the operation key is first set to position *1*; this raises all the pointers to the horizontal. Assume that the proposition to be fed in is $A\ b \prec 0$ (i.e. $A \supset B$): we press the letter key A; this has no visible effect. The operation key is set to position *3*, which causes all pointers except the a's to fall and then to position *2*; this sustains the a's at the horizontal. Letter key b is then pressed and the operation key set to position *3*. On the dial plate the $A\ b$ pointers fall to the vertical. We may thus continue to impress as many of the premises of a problem as we please until all the pointers have fallen. The conclusion can be read from the fallen (vertical) pointers as a negative expression in the normal conjunctive form, or from the remaining horizontal pointers as a positive expression in the normal disjunctive form. It would appear that the letter keys involved require to be closed while the operation key is set to positions *3* or *2*; this seems to restrict the machine's possibilities.

The actual cardboard diagram in the Princeton Library, of which Fig. 1 is a photostat copy, is in color. Wires extending from the letter keys are colored thus: A brown (probably red faded) a red, B and b blue, C and c green, D and d yellow; the rest of the wiring is in black.

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Radioactive Colloids—Increased Danger

REPORTED recently (*1*) is a technique for recording the anatomic configuration of the liver by means of intravenous injections of radioactive colloidal gold (Au^{198}). The reticulo-endothelial (RE) system will pick up this colloidal matter with 80–90% being taken up by the liver RE cells. Due to the gamma radiation of Au^{198}, the shape and location of the liver may be estimated by measuring the gamma radiation intensity at different points over the skin. Authors of the report used the technique successfully in animal experiments, and they further state . . . "instrumentation developments are currently in progress at this laboratory in an effort to determine if such instrumentation would permit the use of a dose of radioactive colloidal gold which would be fully within the limits of safety for application to human beings."

The "limits of safety" of radiation dosage for RE cells would seem puzzling to the radiobiologist at the present time. Some experimental data published during the past few years suggest that RE cells be considered as one of the highly radioresistant tissues of the body. As much as 300 r (*2*), according to one author, and 800 r (*3*), according to another, whole body x-ray irradiation in rabbits did not alter the phagocytic function of the RE system. However, some recent direct experimental results indicate that RE cells are the most, or at least one of the most, radiosensitive cells of the organism. In rats, 25 r whole body x-ray irradiation considerably impaired RE functions, as reported by our laboratory (*4*). Another factor which has to be borne in mind is that

the radioactive particulate matter is not evenly distributed throughout the liver or spleen, but is concentrated in RE cells. Therefore, the dose of radiation absorbed by RE cells in these organs will be higher than in the case of uniform distribution (*5*). Furthermore, the claim of the earlier literature that there is a rapid regenerative tendency of the RE system based on qualitative histological observations appears not to be confirmed by more recent investigations in this laboratory.

The significant role of the RE system in serum globulin synthesis, antibody production, fat metabolism, infections, general resistance, etc., is fairly well established despite the fact that much more quantitative work is desirable. If one considers the RE system as being highly radiosensitive, it would appear to be a matter of great importance to point out at this time the danger of injecting intravenously radioactive colloids for diagnostic purposes in humans.

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Terminology of Atmospheric Shells

IT might be interesting, in view of the confusion now existing in the terminology of the various atmospheric shells, to indicate the system now employed by the Geophysics Research Directorate. This system considers that the atmosphere is divided into six "spheres" or shells, not necessarily either spherical or concentric. The approximate altitude ranges of these shells and the names of the dividing surfaces are shown in Table 1.

It should be noted that a "dividing surface" may have appreciable thickness and hence not be strictly a surface. In the case of the tropopause, for example, this thickness may be several kilometers and in the case of the chemopause it may, perhaps, be 10 km or more. Figure 1 diagrammatically portrays the nomenclature adopted.

TABLE 1

ATMOSPHERIC SUBDIVISIONS

Atmospheric region	Altitude (km)	Dividing surface*
Troposphere	0–11	Tropopause
Stratosphere	11–32	Stratopause
Chemosphere	32–80	Chemospause
Ionosphere	80–400	Ionopause
Mesosphere	400–1000	Mesopause
Exosphere	Above 1000	

* Between the shell concerned and the next higher shell.

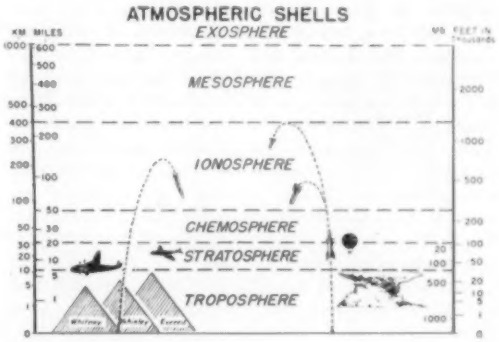

FIG. 1.

The various altitudes given represent mean conditions at middle latitudes.

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Book Reviews

Introduction to Organic Chemistry. Leland A. Underkofler. New York: D. Van Nostrand, 1953. 352 pp. $4.25.

Professor Underkofler's text is designed specifically for very short courses in organic chemistry and for students in colleges of agriculture, home economics, and nursing. As such, much of the detailed treatment considered desirable for science or chemistry majors is omitted. On the other hand, the book is not simply a descriptive exposition of well-known organic materials but includes discussions of carefully selected principles and practices of the science. The interested student will attain a working knowledge of structural chemistry, systematic nomenclature, and synthetic methods. Reaction mechanisms and the electronic concepts of valence and resonance are scarcely considered. Biochemical topics have been kept to a minimum since it is expected that they will be considered in subsequent courses.

Each chapter is concluded with an excellent set of questions and problems. There is an appendix listing organic type reactions and a satisfactory index. The type is large and easily legible and there are very few errors, technical or typographical. The book should prove very desirable for its intended uses.

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A Manual of the Chiggers. The biology, classification, distribution, and importance to man of the larvae of the family Trombiculidae (Acarina). Memoirs of the Entomological Society of Washington, No. 4. G. W. Wharton aided by H. S. Fuller. Washington, D. C.: Entomological Society, c/o U.S. National Museum, 1952. 185 pp. Illus. $6.00.

This book will be a valuable aid to the study of what is probably the least known of the important groups of arthropod pests and disease carriers. It contains sections on the public health importance of chiggers, behavior, life cycles and methods of culturing, anatomy, distribution, and ecology. There is a very extensive bibliography. The bulk of the book, however, is devoted to a catalogue of the known chiggers of the world, with keys to the level of genera and subgenera. Thus the book is not a manual in the usual sense, for no species could be identified with the aid of this work alone; however, it does provide a good general account of the chigger mites together with a most excellent guide to the literature of the world. Localities are given only to country in the catalogue. The usefulness of the work would have been vastly increased had locality data, especially type localities, been more thoroughly treated. This could have been done in only a little more space.

In a work of this scope much is necessarily the result of compilation. It should be pointed out, however, that considerable new material, mostly the result of ecological studies by Wharton and his associates, is included.

Errors are inevitable in a work of this scope. One may be mentioned. It is clearly an error that certain illustrations were credited to "Wharton *et al.*, 1951"; these were prepared and published by D. W. Jenkins and were properly credited to him in 1951. To me it seems unfortunate that, under "Collecting Methods," Lipovsky's washing technique, considered by many as the best way of obtaining chiggers from their hosts, is minimized.

Of far greater importance are criticisms having biological implications. The following comments concern not only this book but all recent American works on these mites, including those from the laboratory of the undersigned.

1. The scheme of terminology for some of the leg setae does violence to all concepts of homology and is likely to be misunderstood. Unbranched setae on the legs are given special names, such as mastitibiala and mastitarsala. The homologous setae, if branched, are not so designed. Thus if a couplet in a key should read "mastitarsala present" and "mastitarsala absent" it would really mean only that a certain seta is simple in the first instance, branched in the second, not that a certain seta is present or absent. It will be difficult to homologize all leg setae but at least we should avoid deceptive terminology. The use of expressions like "sensory setae" is also dubious, since probably all the setae have sensory functions.

2. Relationships are best indicated by considering the chiggers as one of the several subfamilies of Trombidiidae rather than singling them out for elevation to family rank merely because they happen to have received recent intensive study as parasites of vertebrates and as disease vectors. Wharton's subfamilies would then be called tribes of the subfamily Trombiculinae.

Such shortcomings as these result largely from our meager knowledge of the group and some of them could scarcely have been eliminated from a comprehensive work on chiggers at this time. The authors are to be congratulated on a very useful contribution.

CHARLES D. MICHENER
Department of Entomology, University of Kansas

Scientific Book Register

Order-Preserving Maps and Integration Processes. Annals of Mathematics Studies, No. 31. Edward J. McShane. Princeton, N. J.: Princeton Univ. Press, 1953. 136 pp. $2.75.

Luminescence and the Scintillation Counter. S. C. Curran. New York: Academic Press; London: Butterworths, 1953. 219 pp. Illus. $5.80.

Volcanoes as Landscape Forms. Rev. ed. C. A. Cotton. New York: Wiley, 1952. 416 pp. Illus. + plates. $9.00.

Plant Morphology. Arthur W. Haupt. New York–London: McGraw-Hill, 1953. 464 pp. Illus. $8.00.

Disease and Its Conquest. G. T. Hollis. New York: Oxford Univ. Press, 1953. 163 pp. $2.50.

La Pensée Artificielle: Introduction à la Cybernétique. Pierre de Latil. Paris: Librairie Gallimard, 1953. 332 pp. Illus. + chart. 890 fr.

Conferences on Drug Addiction Among Adolescents. Sponsored by the Committee on Public Health Relations of the New York Academy of Medicine. New York–Toronto: Blakiston, 1953. 320 pp. $4.00.

Kernel Functions and Elliptic Differential Equations in Mathematical Physics. Stefan Bergman and M. Schiffer. New York: Academic Press, 1953. 432 pp. Illus. $8.00.

Progress in Metal Physics, Vol. IV. Bruce Chalmers, Ed. New York: Interscience; London: Pergamon Press, 1953. 403 pp. Illus. + plates. $9.00.

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Philosophy: An Introduction. Archie J. Bahm. New York: Wiley; London: Chapman & Hall, 1953. 441 pp. Illus. $4.50.

Outlines of Structural Geology. 3rd ed. E. Sherbon Hills. New York: Wiley, 1953. 182 pp. Illus. + plates. $3.00.

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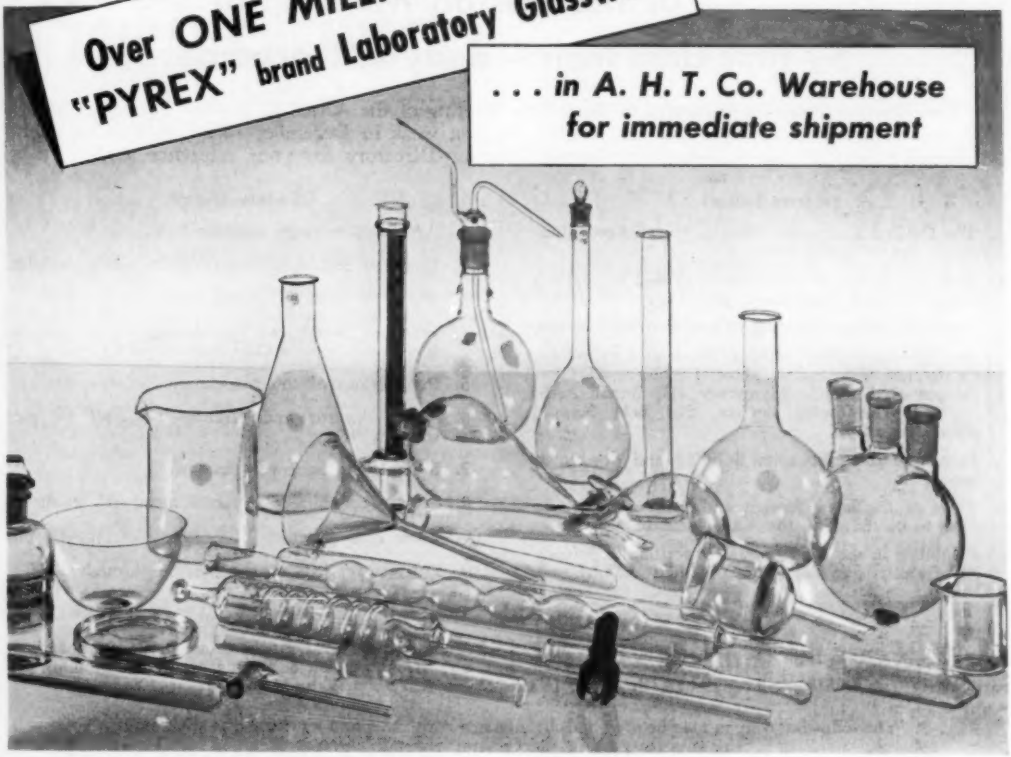

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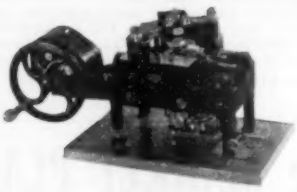

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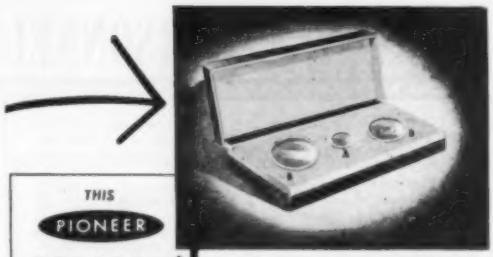

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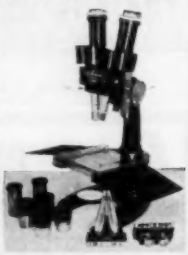

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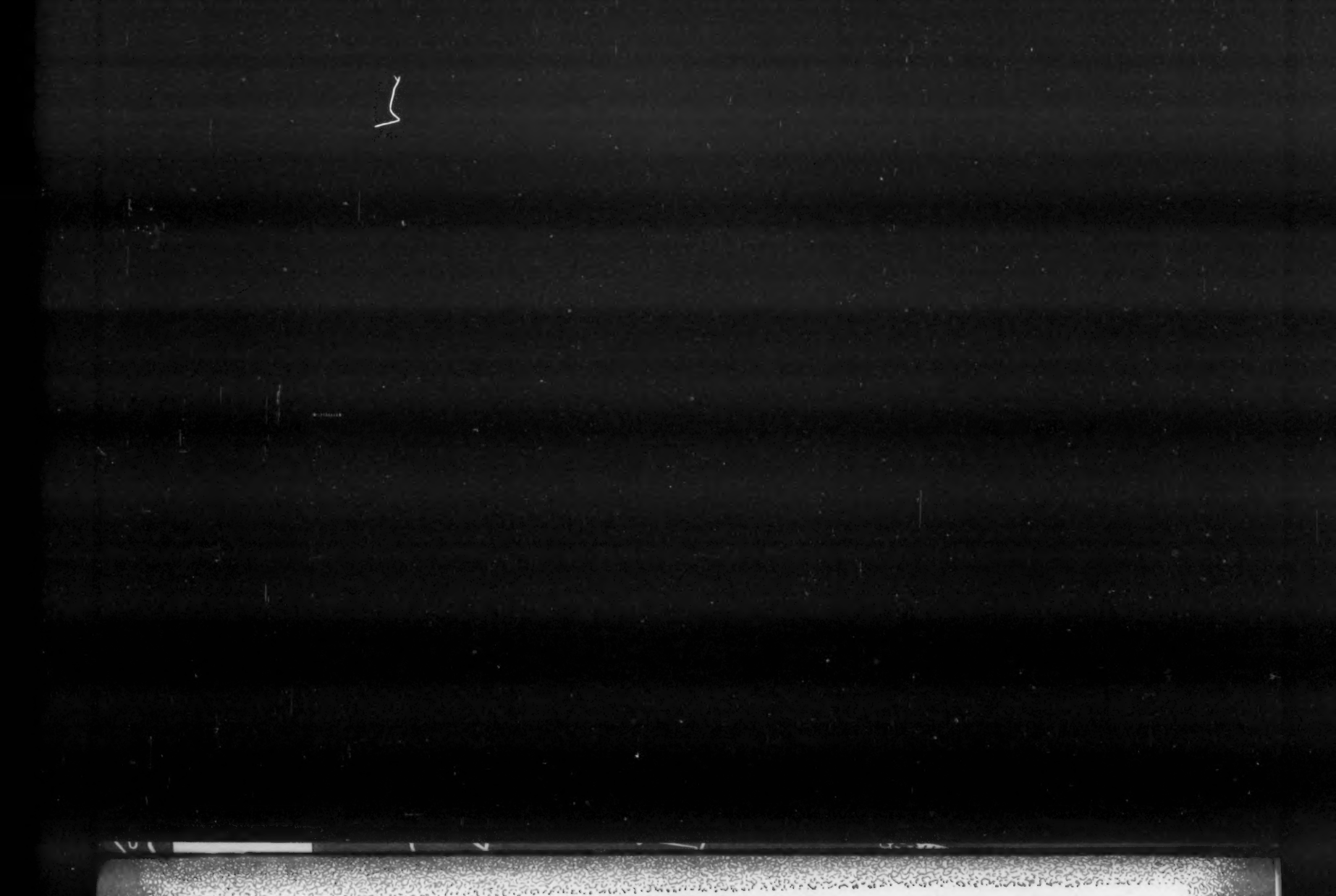
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